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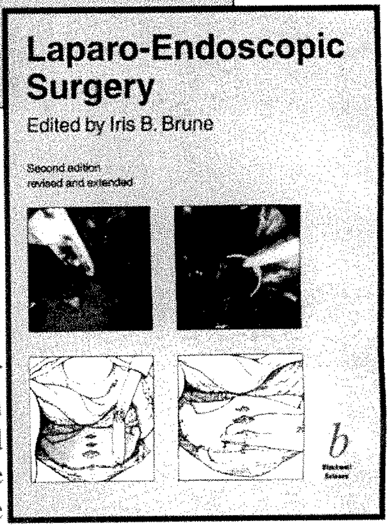

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Leading articles

Helicobacter pylori and peptic ulcer surgery

A decade ago no one considered that peptic ulceration was an infectious disease. Now it is known that *Helicobacter pylori*, a motile flagellate bacillus which dwells in the mucous layer of the stomach, is the main culprit of peptic ulceration. These bacteria are found in over 90 per cent of patients with duodenal ulcer and about 70 per cent of those with gastric ulcer. If the bacteria are eradicated, ulcer recurrence is dramatically reduced[1]. Indeed, healing of both duodenal[2] and gastric[3] ulcers can be achieved with eradication alone, without the addition of acid suppression. For the first time peptic ulcers can be cured medically without the need for long-term maintenance therapy. Such new information has not only revolutionized thinking on the pathogenesis of peptic ulceration, it has also forced a reconsideration of treatment policy. Indications for peptic ulcer surgery and the choice of ulcer operations must be revised in the light of these new discoveries.

Because *H. pylori* is protected by the mucous layer of the stomach, its eradication requires multiple drugs to be administered simultaneously. The original triple therapy regimen uses bismuth salts; side-effects and patient compliance are common problems. Newer regimens use a proton pump inhibitor combined with two antibiotics and may be administered on a twice-daily basis; side-effects are less common and high rates of eradication of over 90 per cent may be achieved with 1 week of treatment[4].

If long-term cure can be achieved with a 1-week course of tablets, it makes little sense to offer elective ulcer surgery to patients without first attempting a medical solution. Only patients who fail to achieve eradication after multiple attempts and those who are *H. pylori* negative should be considered for surgery. Such patients are rare indeed and elective ulcer operations are now becoming extinct. Surgery for peptic ulcer in the new millennium will be confined to dealing with complications.

Bleeding is the commonest complication of peptic ulceration. In the past decade endoscopic haemostasis has superseded surgery as the first-line method directed at stopping ulcer bleeding. There is now good evidence that recurrent ulceration and bleeding can be prevented by *H. pylori* eradication[5]. Several studies, including two randomized controlled trials, have shown that after eradication the rebleeding rate over a follow-up of up to 1 year is zero, compared with 15–30 per cent in those who have not had eradication. Eradication therapy has also been shown to be superior to long-term maintenance with histamine receptor antagonists[6]. With effective endoscopic methods of stopping bleeding and the knowledge that medical cure of the ulcer diathesis is possible, the temptation is to persist with endoscopic therapy, especially in elderly patients. This may be dangerous as repeated blood loss, hypovolaemia and multiple transfusions lead to poor outcome. A well organized gastrointestinal bleeding team with clearly defined guidelines and endpoints is of vital importance in achieving good results.

The aggressive use of endoscopic haemostasis leads to a smaller proportion of patients requiring emergency surgery. Those who do are likely to be elderly and to have concomitant medical illnesses. They tend to have lost significant amounts of blood as they typically will have had one (or two) unsuccessful attempts at stopping bleeding by endoscopy. Such patients present a difficult challenge for the new generation of surgeons, who have not had the opportunity to experience many elective gastric resections The aim of emergency surgery should be to control the bleeding securely, rather than to prevent ulcer recurrence. Whether gastrectomy or a more conservative approach (under-running of the ulcer, with or without vagotomy and drainage) is superior has been hotly debated over the years. The conservative option is technically less demanding but carries a higher risk of rebleeding in the immediate postoperative period. In practice the choice of operation is determined by the size of the ulcer; small ulcers (less than 2 cm) may be safely under-run (or excised) with little risk of rebleeding, but giant ulcers that penetrate into the pancreas require a technically difficult gastrectomy

For patients with perforated peptic ulcer the conventional treatment is urgent laparotomy and an omental patch repair. For those under 40 years of age, conservative non-operative management is effective[7]. However, with the laparoscopic revolution, laparoscopic patch repair has become relatively easy and should be within the competence of most general surgeons[8]. Definitive ulcer operations on the other hand, especially in the emergency setting, are likely to be attempted by only a few enthusiasts. Seventy per cent of perforated duodenal ulcers harbour *Helicobacter* infection. Such infection is associated with a higher preponderance of males, dyspepsia, and a much lower incidence of non-steroidal anti-inflammatory drug usage (5·9 per cent) than that found in non-infected patients (45 per cent)[9]. This suggests that perforations caused by *H. pylori* and non-steroidal anti-inflammatory drugs may be two distinct entities, and supports a policy of patch repair followed by eradication of *H. pylori* in those who are infected.

Mechanical gastric outlet obstruction due to chronic scarring from peptic ulceration classically required operative intervention. Non-operative treatment with balloon dilatation has met with limited success; recurrent ulceration and reobstruction occurred in up to 50 per cent of patients after a 3-year follow-up[10]. There is little information on the relationship between *H. pylori* and peptic pyloric stenosis. In the authors' unit the incidence of *H. pylori* infection in patients with pyloric stenosis is around 50 per cent (unpublished data). Resolution of gastric outlet obstruction after eradication of infection has been reported[11]. Whether balloon dilatation plus eradication is adequate treatment for patients with gastric outlet obstruction associated with *H. pylori* infection awaits further study.

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Parotid pleomorphic adenoma

Most discrete parotid lumps are salivary neoplasms and 80 per cent of these are benign pleomorphic adenomas. During the first half of this century the treatment of pleomorphic adenomas was distinguished by fear of damage to the facial nerve, and mystery surrounded the pathology of these tumours. The combination of a myxochondroid component and the slow-growing nature of the lesions led to the belief that they were teratomas (mixed parotid tumours) and not true neoplasms. Surgical treatment consisted of simple enucleation through an incision directly over the mass, but by the 1930s it was apparent that the recurrence rate associated with such management was 20–45 per cent.

In the 1940s, with Hamilton Bailey as one of its proponents, the facial nerve was dissected in order to preserve it and superficial parotidectomy started to be practised. By 1957 an explanation was put forward for tumour recurrence by Patey and Thackray[1], who demonstrated that small tumour buds protrude from the tumour surface into a surrounding pseudocapsule. Despite being widely accepted at the time, the theory that these tumour buds were mainly responsible for the propensity of the tumour to recur was to be proved wrong. The evidence for this was provided by Nicholson and Gleave, who for 45 years used 'extracapsular dissection' in close proximity to the tumour surface with results that were equally as good as those of superficial parotidectomy[2]. This also explained the paradox that preserving the facial nerve added no risk of recurrence despite the fact that 50 per cent of nerves were in direct contact with the tumour capsule. It became apparent that the main responsibility for recurrence lay with the surgeon.

The annual incidence of parotid pleomorphic adenoma in the UK (population $5{\cdot}7 \times 10^7$) is about $1{\cdot}4 \times 10^5$ and the favoured site is the tail of the parotid (60 per cent), with the majority of tumours lying superficial to the facial nerve. An asymptomatic lump is the normal mode of presentation but occasionally there may be pain and, rarely, a facial palsy. Delay in presentation of approximately 2 years is the norm but, even so, parotid tumours greater than 5 cm in diameter are uncommon in Western society. In long-standing tumours (presumably pleomorphic adenomas) there is a propensity for malignant transformation but this is fortunately rare.

The diagnosis is clinical; computed tomography, magnetic resonance imaging or ultrasonography seldom alter management, although the first of these may help delineate the rare tumour that lies deep to the mandible. Similarly, fine-needle aspiration cytology has limited application: it does not usually influence treatment of the apparently benign lump[3] as the surgical management of both pleomorphic adenoma and low-grade cancer is the same. This amounts to some form of superficial or total parotidectomy, depending on the size and site of the tumour, with nerve preservation; surgery is followed by radiotherapy under appropriate circumstances[4,5].

Apart from injury to the facial nerve the complications of parotid surgery are minor. They comprise neuroma, Frey's syndrome and fistula. Following superficial parotidectomy, permanent nerve injury occurs in about 1 per cent and transient paresis in about 30 per cent of patients[2]. After total parotidectomy, the incidence rises to 6 and 60 per cent respectively[6]; 90 per cent of transient injuries recover within 12 months. Tumour recurrence should be less than 2 per cent at 10 years[2,7,8].

Recurrent pleomorphic adenoma occurs in patients whose age at initial presentation is about 10 years less than that of those with pleomorphic adenoma in general (32 *versus* 47 years)[9]. It has been suggested that this is because it represents a more aggressive tumour, but this is probably not so for, if adequately treated, recurrence reaches a plateau at 15 per cent[9]. Norman[10] has suggested that there may be a reluctance to undertake a comprehensive procedure in a young person, leading to an increased risk of disease recurrence. Treatment of recurrent disease poses a significant risk to the facial nerve. Permanent injury occurs in 15 per cent of patients after a second operation and in 30 per cent after a third[9], although in practice the risk depends on the extent of previous surgery. In old or infirm patients with recurrent pleomorphic adenoma proven by aspiration cytology, there is a good case for avoiding operation. Recurrence is either uninodular or multinodular, and the distinction is important. When uninodular disease is treated by surgery alone there is a 15 per cent recurrence rate at 15 years; with multinodular disease the failure rate is 43 per cent. Adjuvant radiotherapy in this latter group limits recurrence to 4 per cent[9], but with a risk of radiation-induced malignant change. This risk may be overstated for, in the Christie series[9], no malignant degeneration occurred in parotid adenomas treated successfully for first recurrence with surgery plus radiotherapy, but rather in those subjected to multiple operations.

Looking back over a century of surgical effort, the mystery surrounding 'mixed parotid tumour' has been unravelled. The natural history and appropriate management have been clarified, outcome measures set and risks of surgery quantified. The century closes on a now well delineated topic.

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Review

Preventing postoperative recurrence of Crohn's disease

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Background and methods Risk factors for recurrence of Crohn's disease and the evidence for progress in reducing recurrence following resection were reviewed. A Medline based literature review was carried out.

Results and conclusion Only smoking has been confirmed as a significant adverse risk factor for recurrence. Evidence for differing recurrence rates in fibrostenosing disease and perforating disease is inconclusive, but such a classification along with the endoscopic findings of recurrence may have a place in the analysis of therapeutic trials. Minimal resectional surgery with clearing of only macroscopic disease seems to be justified, with no clear benefits from different anastomotic techniques Recent trials offer encouraging evidence of the usefulness of 5-aminosalicylic acid, particularly higher-dose regimens started early after resection, although the long-term benefits are uncertain. The oral steroid, budesonide, offers a potent treatment with minimal side-effects, but evidence of its prevention of recurrence is presently weak.

That Crohn's disease is a relapsing condition with a strong tendency to recur has been noted since its description[1]. The recurrent nature of the disease can bedevil both patients and doctors, physicians and surgeons alike, with the ever present threat of the risk of further symptoms, further treatment and the need for further surgery. Recurrence rates and risks have been studied almost since the disease was recognized in an attempt to gain insight into the nature of the problem, its cause, and appropriate methods of medical and surgical treatment. More recently, endoscopic study of early changes in the bowel after surgery and the evolution of drug therapies have led to renewed interest in attempts to alter the clinical course of the disease.

This paper reviews the many studies focusing on assessment of recurrence risk and the factors associated with it. The surgical and pharmacotherapeutic options available to minimize the chance of recurrence are assessed, particularly in the light of recent research.

Study of recurrence – the key tools

The natural history of Crohn's disease is characterized by chronicity and varying degrees of symptom recurrence, radiological recurrence and the need for surgical intervention. The study of recurrence has been progressively unified and standardized by the development of several key outcome measures and the adoption of common appropriate statistical methods. The surgical and histopathological definition of Crohn's disease has been established for years following the published work of Morson[2], Farmer *et al.*[3], Lockhart-Mummery and Morson[4], Lennard-Jones and Stalder[5,6], and Lee and Papaioannou[7]. These criteria have enabled studies to exclude previously confounding diagnoses, such as indeterminate colitis. The endpoint of recurrent disease leading to symptoms sufficient to justify resection conveniently defines the reoperation recurrence rate. This, however, is a measure of only the most symptomatic recurrences. The development of the Crohn's Disease Activity Index (CDAI)[8] has enabled a greater degree of uniformity and standardization to be applied to the previously difficult area of defining symptomatic relapse. The widespread adoption of criteria such as 'CDAI greater than 150 and rise of 100 points confirmed over a 2-week period' allows studies using largely equivalent endpoints to be compared. The elegant work of Rutgeerts *et al.*[9,10] has introduced a widely accepted endoscopic scoring system which has been shown to be reproducible between different observers[11]. This has highlighted the concept of 'endoscopic recurrence', permitting the study of these appearances of recurrence in the shorter term.

Given the long periods over which Crohn's disease recurs, the widespread introduction of actuarial (Kaplan–Meier) and life-table methods as the most appropriate tools for the assessment of recurrence[12–14] has allowed comparison of relapse rates over the long term. The unification of the defining features of outcome and the use of more appropriate statistical methods have together provided improved yardsticks to assess trials of therapy.

Size of the problem

Recurrence after surgery for Crohn's disease is almost inevitable. Data from a large number of studies are shown in *Tables 1* and *2*[17]. Figures are harvested from papers confined to the study of recurrence following 'curative' surgery at which all macroscopically diseased bowel was resected with a primary anastomosis performed and the location of resected disease clearly defined. Microscopic disease may be found in macroscopically normal bowel[28,29], but considering studies of macroscopic 'curative' resection allows the best opportunity to compare broadly similar groups which have been rendered 'disease free' largely to the same extent. It is a convenient way of obtaining a relatively homogeneous patient group, rather than the involved study of patients with lesions of mixed ages and

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Table 1 Recurrence rates defined by reoperation according to location of resected disease

Reference	Year	Study period	Resection site	*n*	Recurrence rate (%) 5 years	10 years	15 years	20 years
Wettergren and Christiansen[15]	1991	1961–1987	ic	48	11	30	48	
Heen *et al*[16]	1984	1962–1978	ic	66		36		
Nordgren *et al.*[17]	1994	1969–1977	ic	68	22	38	46	52
Lock *et al.*[18]	1981	1955–1973	ic	146	27	44	50	
Whelan *et al.*[19]	1985	1966–1969	ic	224			53	
Hellberg *et al.*[20]	1980	1968–1977	ic	55		36		
Sayfan *et al.*[21]	1989	1950s	i+ic	41	26			
Higgens and Allan[22]	1980	1944–1979	i+ic	227	18	36	51	55
Lock *et al.*[18]	1981	1955–1973	i	108	17	32	38	
Whelan *et al.*[19]	1985	1966–1969	i	104			44	
Hellberg *et al.*[20]	1980	1968–1977	i	41		22		
Nordgren *et al.*[17]	1994	1969–1977	c	66	32	42	46	46
Lock *et al.*[18]	1981	1955–1973	c	107	11	20	32	
Whelan *et al.*[19]	1985	1966–1969	c	104			41	
Hellberg *et al.*[20]	1980	1968–1977	c	39		32		

ic, Ileocolic; i, ileal; c, colonic

Table 2 Recurrence rates defined by reoperation, symptom, radiological or endoscopic criteria according to location of resected disease

Reference	Year	Study period	Resection site	Criteria for recurrence*	*n*	Recurrence rate (%) 5 years	10 years	15 years	20 years	25 years
Wettergren and Christiansen[15]	1991	1961–1987	ic	S or R	48	38	52	79		
Heen *et al.*[16]	1984	1962–1978	ic	S and R	66	55	76			
Lindhagen *et al.*[23]	1983	1958–1974	ic	R or E	102			52		
Pallone *et al.*[24]	1992	1972–1986	ic	S and R/E	58	42				
Hellberg *et al.*[20]	1980	1968–1977	ic	R	55		42			
Trnka *et al.*[25]	1982	1942–1972	ic	O or R	40	29	42	62	72	79
Raab *et al.*[26]	1996	1969–1986	ic	R or E or O	82	28	51	60		
Pareja *et al.*[27]	1996		i+ic	S and R/E	107	30	49	59		
Hellberg *et al.*[20]	1980	1968–1977	i	R	41		57			
Trnka *et al.*[25]	1982	1942–1972	i	O or R	67	18	40	56	73	79
Raab *et al.*[26]	1996	1969–1986	i	R or E or O	147	17	32	51		
Hellberg *et al.*[20]	1980	1968–1977	c	R	39		42			
Raab *et al.*[26]	1996	1969–1986	c	R or E or O	55	30	41	45		

*Recurrence was defined with respect to symptoms (S), radiological (R) or endoscopic (E) criteria, or reoperation (O). ic, Ileocolic; i, ileal; c, colonic

histories. Differing policies regarding the timing of surgery may be a confounding factor; some units pursue an aggressive line favouring early surgery and so select a group of patients earlier in the course of their disease. Such policies, however, are unlikely to result in widely dissimilar groups. In any event, there is good evidence that length of time from diagnosis to first operation does not alter the risk of subsequent recurrence or time to recurrence[20,22,25,30,31].

Table 3 summarizes these data and indicates that the risk of recurrence for ileal and ileocolic disease, by symptomatic or radiological criteria, rises from 18–55 per cent at 5 years to 40–76 per cent at 10 years, 52–76 per cent at 15 years, and 72–73 per cent at 20 years. For recurrence sufficient to precipitate reoperation, the rate progressively and continually rises with time from 11–27 per cent at 5 years to 30–44 per cent at 10 years, and 48–53 per cent at 15 years. There is substantial agreement between studies in which reoperation is the defined endpoint.

Factors associated with recurrence

An extensive review of factors associated with recurrence has been published previously[32]. Early studies in the search for predictors of recurrence focused on factors which might allow patients at higher risk to be identified.

Age

Many studies have analysed data according to age. Several have shown no clear effect of age of onset of the disease (as judged by age at onset of symptoms consistent with Crohn's disease) on subsequent recurrence rate[10,20,22,25]. Some authors have suggested a highest risk of recurrence in younger patients[33-35], others in an older group[27]. Where an effect of age on early recurrence was noted, reports have suggested a diminution of this adverse feature over the longer term[36,37]. In summary, age does not appear to be a clear predictor of recurrence risk.

Table 3 Overall estimation of risk of recurrence in ileal and ileocolic disease

Length of follow-up at which risk assessed (years)	Symptomatic &/ radiological recurrence (%)		Reoperative recurrence (%)	
	Range of risk†	'Weighted average risk'*	Range of risk†	'Weighted average risk'*
5	18–55	34·8	11–27	20·3
10	40–76	50·5	30–44	36·0
15	52–76	59·5	48–53	48·5
20	72–73			
25	79			

*Arbitrarily calculated by *n*-weighted average of risks quoted; †lowest and highest risks reported

Sex

Several studies have indicated that there is no difference in recurrence risk between the sexes[10,20,25,38,39], although there is a worsening of the adverse effects of smoking among female *versus* male smokers (*vide infra*).

Site of disease

Analysis by site of disease (ileal *versus* ileocolic *versus* colonic) has generally revealed no significant difference in recurrence rate[18–20,23,25,40,41]; some studies have suggested a worse prognosis for ileal disease[26,42], ileocolic disease[43] or colonic disease[37]. The extent of surgery may be a confounding factor. On balance, a marginally lower recurrence rate may be inferred for colonic disease, but this is unproven.

Length of history

The influence of the length of history before resection has been a vexed issue[32], complicated by recall bias, accuracy of retrospective prediagnosis data collection, and dealing with time as a continuous variable. The bulk of reports describe no association between disease duration and recurrence risk[9,10,18,20,22–25,30,31,37,40]. Some studies have shown a higher risk with disease of longer duration[44,45] and others a higher risk with disease of short duration[33]; one even describes a marginally increased risk in disease of intermediate (3–10 years) duration[46]. It seems safe to assume there is no certain relationship between preoperative duration and recurrence.

Smoking

The influence of smoking on the course of Crohn's disease is complex. Retrospective studies inherently suffer from recall bias during data collection. The differing definition of what constitutes an 'ex-smoker' and the continuous nature of the variable 'number of cigarettes smoked' both make for substantial difficulty in interpreting data from different sources. Despite these limitations, several authors have shown an increased risk of Crohn's disease in smokers compared with non-smokers[47–52], the relative risk being between 1·33 and 4·99 with the highest values occurring in female patients[50]. Other groups have suggested that this significantly increased risk extends to recurrence after operation (either endoscopic, symptomatic or 'reoperative')[53,54]. Interestingly, an Italian study[53], which failed to show any difference in primary diagnosis between non-operated ex-smokers (ceased smoking more than 12 months before operation) and either smokers or non-smokers, found a marked difference in recurrence between the smokers and non-smokers (73 *versus* 40 per cent symptomatic, $P < 0·006$; 70 *versus* 35 per cent with endoscopic signs; and 24 *versus* 8 per cent requiring reoperation, $P < 0·005$). In addition, symptomatic recurrence was greater in those who smoked more than 15 cigarettes per day compared with those who smoked fewer than 15 cigarettes per day, which supports the data of Sutherland *et al.*[54] suggesting an additional dose–response relationship. No apparent difference was noted according to the indication for surgery, whether perforating or non-perforating, giving no clue about the mechanism of the effect of tobacco on the disease. It may be that any difference in effect between such groups is small and the heterogeneity of the non-perforating group may be a confounding factor (no data were published for these groups in either study). Advising patients that smoking is an adverse risk factor for recurrence seems justified, but its effect on different subtypes of disease is an area worthy of specific study.

Other factors

Several other factors have been considered to be associated with an increased risk of recurrence. Intestinal permeability has been related to symptomatic recurrence[55] and α_1-antitrypsin excretion has been related to radiological but not symptomatic or surgical recurrence[56]. An increase in ileal mucosal phospholipase A_2 activity may precede endoscopic recurrence[57] which helps to explain the putative role of enteral lipid in control of symptomatic recurrence[58]. It seems likely that such observations reflect subclinical manifestations of the diffuse disease process but may not necessarily indicate an altered risk of recurrence or direct efforts at its reduction. Perioperative and postoperative blood transfusion was initially thought to be associated with a reduced risk of recurrence[59,60] but several subsequent studies have not supported this notion[51,61–63].

'Type' of disease

Aggressive/indolent

There has been speculation about biologically different forms of Crohn's disease since the earliest series. The biphasic time pattern inferred by de Dombal *et al.*[33] has had support from other studies[46,64] and raises the question of aggressive and indolent forms of the disease. However, retrospective studies are plagued by problems of interpretation of recorded data, particularly indications for surgery, as well as the frequent co-existence of multiple disease patterns in any given patient. Other studies have shown only certain highly selected subgroups as being at higher risk[65,66] and several have shown no difference either in the risk of reoperation or time to reoperation according to the indication for primary operation[18,31,67]. At present, there is no clear indication that Crohn's disease may be divided meaningfully into two forms according to speed and severity of recurrence. Indeed, there is a substantial amount of evidence to suggest that second and third recurrences occur at similar rates to first recurrence, whatever the indication for initial surgery[22,25,68–70].

Perforating/non-perforating

The Mount Sinai group suggested that Crohn's disease may be classified into two distinct clinicopathological types: 'perforating' and 'non-perforating'[69]. In a retrospective analysis of patients after resection, indications for surgery were classified as perforating or non-perforating on the basis of the presence or not of certain clinical, radiological or pathological features of perforation. From these data, the group found that there was a highly significant similarity in indication in those patients undergoing second and subsequent resections, compared with the indication for initial operation. The data also suggested that, while the risk of recurrence between the two groups was similar, the time to reoperation was shorter in the 'perforating' group. They concluded that this was evidence for two clinical forms of the disease with preservation of disease 'phenotype' in individual patients. The study, however, was confounded by the heterogeneity of the 'non-perforating' group and the inclusion of patients into the 'perforating' group on the basis of presence of the perforating criteria, even if other features were present or even predominant. In particular, perianal fistulating disease was included in the perforating group with or without evidence of abdominal disease. Studies from Rome[24] and Yokohama[71] have examined obstructing indications for surgery and have demonstrated a significant correlation between indications for first and second resections. The Cleveland Clinic data[72], however, do not support the view that 'preservation of clinical disease type' occurs within individual patients. No similarity to initial operative indication was found in indications in reoperated patients, and no difference was found in risk or speed of recurrence. Indeed a more recent retrospective study of the Mount Sinai patients, in which they were classified into 'fistulizing' and 'fibrostenotic' disease types, failed to show any significant difference in rate of or time to reoperation between the two groups[70]. In a report from Holzheimer *et al.*[66], only acute free perforation correlated with increasing risk of recurrence but the number studied was small ($n = 14$) and acute, free perforation is a very limited definition upon which to base the classification of a 'perforating' subtype of disease. Data from a multicentre randomized controlled trial[31] and a prospective study[30] using endoscopic appearances as endpoints failed to demonstrate differences in recurrence rates between perforating and non-perforating indications for initial resection, although the criteria for these definitions were not clear.

Thus the evidence favouring two disease patterns which are conserved within patient groups is mixed. There is no clear evidence to support the view that one or other indication for initial operation is associated with any greater risk of, or shorter time to, recurrence. It is important to clarify this issue since the outcome of medical therapies may differ significantly between types of disease. Analysis of therapeutic trials on the basis of reliably classified 'inflammatory/fistulizing' and 'obstructive/fibrostenosing' disease may allow a demonstration of efficacy in one or other subgroup where overall analysis might fail to show any difference.

Endoscopic recurrence

The neoterminal ileum after ileocaecal resection is accessible by ileocolonoscopy and provides a 'model' for the study of recurrence. One of the original papers by Rutgeerts *et al.*[9] described the features of endoscopic recurrence in the neoterminal ileum following ileocolic resection; these have since been extended and form the basis of a reproducible and widely adopted scoring system[10].

Several key features have arisen from the endoscopic work. The predilection of recurrence in the pre-anastomotic area of the neoterminal ileum has been confirmed repeatedly. Recurrence occurs at this site in 70–100 per cent of cases[9,10,24,73] Not surprisingly, the early endoscopic recurrence rate (72 per cent at 1 year) is higher than that obtained by using any other endpoint, but there is no apparent significant increase in endoscopic recurrence thereafter, with rates at 1–3 years and more than 3 years of 79 and 77 per cent respectively. This suggests not only that endoscopic features precede all other indicators of recurrence but also that such features are present either by 1 year or not at all.

Of great significance is that, in a prospective study of 89 macroscopically 'curative' ileocolic resections for isolated ileocolic disease (a homogeneous, strictly followed group)[10], endoscopic recurrence (as defined by a score of i,1 or greater (*Table 4*)) was highly predictive of subsequent symptomatic and surgical recurrence ($P < 0{\cdot}0001$), even when stratified for preoperative CDAI. In addition, the endoscopic score itself at 1 year after operation (i,1 *versus* i,3/i,4) was highly predictive of the subsequent rate of recurrence and time to recurrence. This evidence is supported by a smaller, less rigorous study[30] which used a slightly different, although similar, classification of endoscopic findings; it showed similar endoscopic recurrence rates, and a relationship between endoscopic score and subsequent symptom presentation. The study by de Jong *et al.*[74] did not find any correlation between endoscopic scores at 1 year and reoperation rates, although no analysis was made for recurrence in different subgroups according to grading of endoscopic findings. No symptomatic recurrence data were gathered and surgical recurrence was studied only up to 8 years, which is a relatively short period for a phenomenon which occurs

Table 4 Scoring of endoscopic recurrence after ileocolic resection[10]

Score	Lesions present
i,0	No lesions
i,1	Fewer than five aphthous lesions
i,2	More than five aphthous lesions with normal mucosa between the lesions or skip areas of larger lesions confined to the ileocolic anastomosis
i,3	Diffuse aphthous ileitis
i,4	Diffuse inflammation with large ulcers, nodules or narrowing

i, Ileal

over 25 years. The first two[10,30] of the above three studies are of great importance. If the correlation of early endoscopic findings and subsequent clinical course is correct, endoscopy provides an ideal, early, reliable endpoint for clinical studies into efficacy of therapy, avoiding the need for the long-term follow-up required accurately to determine clinical outcomes.

Surgical factors – margins and techniques

Resection margin

Up to 80 per cent of patients with Crohn's disease require surgical intervention on at least one occasion in the natural history of their disease[34]. It is not surprising, therefore, that there has been considerable interest in the relationship between the nature of surgical intervention and subsequent outcome, particularly with regard to reoperation risk. Despite some evidence to the contrary[16,75], including one recent study from Australia[76] specifically examining the presence of granulomas in resection specimens, the great bulk of evidence indicates that where macroscopic clearance of disease is obtained at resection, microscopic changes or residual histological features of active Crohn's disease at the resection margins have no effect on recurrence[15,16,25,26,44,46,66,68,77–84]. This is supported by evidence that site-specific recurrence after strictureplasty, where, by definition, disease remains at the site of the suture line, is no greater than at other, resected, sites[21,85–87]

Anastomotic technique

Where resection with anastomosis is performed, particularly ileocolic anastomosis, the role of the different possible anastomotic configurations is of interest. Does surgical technique alter patient outcome? A prospective randomized study from Baltimore[88] specifically studied 86 patients with primary ileocolic resection and found no difference between end-to-end and side-to-end anastomosis, either for symptomatic (51 *versus* 51 per cent) or endoscopic/radiological (23 *versus* 31 per cent) recurrence, although the follow-up period was rather short with a mean of 4 years. A long-term follow-up of end-to-end *versus* side-to-side anastomosis from Salford[89] also convincingly demonstrated no difference between techniques, albeit in a retrospective fashion with mixed diagnostic criteria for recurrence. The Gruppo Italiano per lo Studio del Colon e del Retto data[31] suggest a minor disadvantage associated with end-to-end over the three other possible anastomoses (side to end, end to side and side to side) after ileal or ileocolic resection. However, the increased relative risk was only significant in a group treated with anti-inflammatory medication, and the primary objective of the study was not to analyse anastomotic techniques which were simply chosen according to the preference of the surgeon and performed independently in at least four centres. The preponderance of recurrence at the preanastomotic site raises the question as to why the form of anastomosis might matter. Luminal diameter, even in the presence of residual disease, has been suggested as an important factor in precipitating symptoms[90]. In the above studies, all macroscopically evident disease was resected giving intestine of as near normal calibre to anastomose as possible. It is therefore difficult to envisage how an end-to-end anastomosis could produce a significantly narrower lumen than either side-to-end or end-to-side anastomoses. One might expect a side-to-side anastomosis to confer benefit since luminal diameter is easier to preserve or even increase with this method; however, this does not appear to be the case. It is difficult to conceive any difference in faecal stream transit (see below) across the different types of anastomosis to explain the differences in recurrence. Until further evidence is published, it seems reasonable to presume that any anastomosis performed with macroscopically normal bowel using a technique familiar to the operator is as likely to provide as good an outcome as any other.

Faecal stream

The effects of diverting the faecal stream have interested surgeons since studies showed that symptomatic and endoscopic recurrence could be prevented by fashioning a defunctioning stoma proximal to diseased bowel segments[91–93]. That reversal of a defunctioning stoma is associated with prompt endoscopic recurrence has been documented[93], but the fashioning of anastomoses in ways designed to prevent faecal stream reflux into the neoterminal ileum[94] has only weak evidence of long-term benefit. In one study of ileocolic valved anastomoses, the numbers were too small ($n = 6$) to allow any conclusion to be drawn regarding a protective effect of such a valve on the neoterminal ileum. Such an approach has not enjoyed wide application, particularly as there is doubt about the long-term function of such a valved anastomosis[94]. Of interest, however, is that for side-to-end ileocolic anastomoses some data exist which suggest sparing of the short ileal 'blind loop'[88]; this offers further evidence of the role of the faecal stream in disease pathogenesis. That elements of the ileal faecal stream play a part in pathogenesis was strongly suggested by Harper *et al.*[95], and Winslet and Keighley[96] confirmed this to be the case; defunctioning, however, yields only temporary relief of symptoms which is lost after reversal. While such observations add to our understanding of the underlying disease, faecal stream manipulation seems to have only a very limited part to play in surgical intervention.

Medical therapies

Several compounds have a role in the therapy of Crohn's disease. Metronidazole reduces high-grade endoscopic recurrence at 1 year, and both clinical and endoscopic recurrence at 3 years after ileocolic resection[97]. All the benefit, however, occurs in the first year; thereafter actuarial analysis produced parallel recurrence curves in treated and placebo groups. Toxicity may be a significant problem and is likely to limit long-term usage.

Steroids have also been studied after medically-induced remission[98–100], with no observable benefit in the National Co-operative Crohn's Disease Study and the European Co-operative Crohn's Disease Study; a doubtful benefit in reducing relapse was noted in a study by Brignola *et al.*[98] which contained only very small numbers. Immunosuppressive therapy with azathioprine and 6-mercaptopurine may be beneficial for up to 4 years, but with little effect thereafter[101]. This observation, obtained by retrospective analysis, is now being tested in a prospective randomized controlled trial. All of the above drugs, however, have obvious disadvantages in terms of long-term side-effects

Sulphasalazine

The role of the anti-inflammatory agent, sulphasalazine, has been evaluated for postresectional prophylaxis against recurrence in a randomized controlled trial using a dose of 3 g per day[102]. Although the reduction in recurrence was not significant (13 *versus* 45 per cent at 18 months), the study was small, the criteria for diagnosis of recurrence were vague and the length of follow-up was short. The side-effects related to the sulphapyridine moiety of sulphasalazine[103] led to the development of 5-aminosalicylic acid (5-ASA) and in comparative trials this agent was shown to be as good as sulphasalazine and of possible benefit in ileal/ileocolic Crohn's disease[104].

5-Aminosalicylic acid

Several recent studies have been published on the efficacy of 5-ASA preparations (mesalazine, Asacol (SmithKline Beecham Healthcare, Weybridge, UK), Pentasa (Yamanouchi, West Byfleet, UK)) in prevention of recurrence. The data, including dose, follow-up period and endpoint used, are shown in *Table 5*. A number have studied the efficacy of preparations in maintaining remission in quiescent Crohn's disease[107–110]. A major problem is the difficulty in reliably accumulating populations in whom Crohn's disease is clearly inactive and of equivalent distribution. A long period of clinical symptomatic remission before entry into the study was the usual criterion used but the extent of disease was not always assessed. Radiological demonstration of extent of disease was only attempted to any extent by Prantera *et al.*[109] and all workers inherently assess patients who have Crohn's lesions of varying age and activity. In addition, all researchers have used symptomatic relapse as the endpoint. Although this is a widely used endpoint, the time scales of follow-up were frequently short. Nevertheless, all studies showed a lower relapse rate for the treatment arm, although this was statistically significant in only two[108,110]. In the paper by Gendre *et al.*[110], patients were stratified into arbitrarily 'high-risk' and 'low-risk' groups according to length of remission before the study commenced. The only group to show a significantly higher risk of relapse than others was the untreated 'high-risk' group. The dose of 5-ASA used by these workers was between 1 and 2 g per day. The therapeutic benefit of 5-ASA in reducing clinical relapse at 1 year has been confirmed by meta-analysis[112,113]. Only

Table 5 Randomized controlled trials of 5-aminosalicylic acid in the prevention of recurrence after resection and in patients with quiescent disease

Reference	Year	Patient group	*n*	Regimen*	Site of disease	Endpoint(s)	Follow-up	Recurrence rate (%) 5-ASA	Recurrence rate (%) Placebo	*P*
McLeod *et al.*[72]	1995	After resection	163	5-ASA (3 g per day from 8 weeks after operation)	i, ic, c	S_1+R or E E/R (with or without S)	3 years 3 years	26 60	45 78	0·039 0·016
Brignola *et al*[11]	1995	After resection	87	5-ASA (3 g per day from 1 month after operation)	ic	S_2 $E_{(s)}$ $S_2+E_{(s)}$	1 year 1 year 1 year	16 14 24	23 50 56	n.s. $<0·002$ $<0·004$
Caprilli *et al*[31]	1996	After resection	110	5-ASA (2·4 g per day from 2 weeks after operation)	i	E	3 years	57	83	0·0003
Florent *et al.*[105]	1992	After resection	126	5-ASA (1 5 g per day from 2 weeks after operation)	i or ic	E	12 weeks	50	63	n.s
Fiasse *et al.*[106]	1991	After resection	37	5-ASA (1·5 g per day from 3 months after operation)	ic	S_2 R or E	15 months 15 months	39 33	16 30	n.s. n.s
Brignola *et al.*[107]	1992	Quiescent	44	5-ASA (2 g per day)	i, ic, c	S_2	4 months	52	59	n.s.
Arber *et al.*[108]	1995	Quiescent	59	5-ASA (1 g per day)	i, ic, c	S_2	1 year	27	55	$<0·005$
Prantera *et al.*[109]	1992	Quiescent	125	5-ASA (2·4 g per day)	i, ic, c	S_2	1 year	34	55	just n.s.
Gendre *et al*[110]	1993	Quiescent	163	5-ASA (2 g per day)	i, ic, c (high and low risk)	S_2 O	2 years 2 years	47 (low) 55 (high)	71	$<0·003$
Modigliani *et al.*[111]	1996	Steroid-induced remission	129	5-ASA (↓ steroids)	i, ic, c	Weening success		74	58	0·054

*In all trials 5-aminosalicylic acid (5-ASA) was compared with placebo. Endpoints were: S_1, symptomatic relapse, with symptoms judged to be due to Crohn's disease, S_2, symptomatic relapse, with Crohn's Disease Activity Index above 150 and a rise of 100 points over a 2-week period, R, radiological recurrence, E, endoscopic recurrence (Rutgeert's criteria); $E_{(s)}$, severe endoscopic recurrence (score i,3 or i,4); O, reoperation. i, Ileal; ic, ileocolic; c, colonic; n.s., not significant one paper assessed the effect of 5-ASA on steroid weaning[111] and reported borderline success.

Of greater interest are reports evaluating 5-ASA after resection. There is a considerable degree of similarity between the study groups; patients were all rendered macroscopically free from disease and the majority had ileocolic disease resected. Preliminary results using 5-ASA 1·5 g per day failed to show any reduction in recurrence rate[105,106]; the report from Fiasse *et al.*[106] contained only a small number of patients. Three studies using higher doses of 2·4–3 g per day[11,31,72] found reductions in recurrence which were highly significant, particularly using endoscopic endpoints with follow-up ranging from 1 to 3 years. The data from the Italian group[11] showed a reduction particularly in the highest grades of endoscopic recurrence (i,3 and i,4) which, as previously stated, may be most predictive of further progression to symptomatic disease. Of interest is that the greatest reduction (57 per cent treated *versus* 83 per cent untreated) occurred in the group whose treatment was commenced within 2 weeks of resection[31]. All three studies give fairly convincing evidence that there may be a role for 5-ASA preparations in reducing the risk of endoscopic recurrence following resection. The data suggest that high-dose therapy early in the postoperative period may be the most effective regimen.

A real uncertainty lies in the appropriateness of extrapolation of these endoscopic findings to the longer-term aim of preventing recurrence of symptoms and reoperation over 5–15 years. Nevertheless, the evidence suggesting that early endoscopic findings predict the later clinical course supports such an extrapolation. An additional uncertainty occurs because there is no published evidence about whether early effects might need to be sustained with longer-term prophylactic therapy and over what period this might prove to be necessary. Several reports, using both high- and low-dose regimens, describe a low profile of excess side-effects in the treatment groups, which is encouraging for the development of longer-term dose schedule trials. Indeed, there is some evidence that 4-ASA may be as effective as 5-ASA, with a theoretically safer side-effect profile[114]; this may offer a possible alternative therapy for long-term use.

Budesonide

Considerable interest has been generated by a new steroid, budesonide, which has several characteristics that make it particularly suitable for study as a long-term anti-inflammatory agent in Crohn's disease. It has a high first-pass hepatic metabolism and high steroid receptor affinity. Controlled release formulations that deliver high ileal concentrations of the drug taken orally produce considerable topical anti-inflammatory activity with much reduced systemic toxicity[115–117].

A dose ranging study from Canada using a 6 mg *versus* 3 mg *versus* placebo plan for 1 year in ileocolic disease during remission[118] demonstrated an early reduction in symptomatic relapse in the 3-mg and 6-mg treatment groups (greater in the 6-mg group) but the effect was not sustained over 1 year. Similar findings favouring a higher dose of budesonide are described in a European trial[119]. Both studies, however, involved patients who had undergone previous treatment with budesonide (Canadian) or prednisolone (European) at varying doses for acute, symptomatic Crohn's disease. The patients had thus been rendered inactive as defined by the CDAI. The apparently short length of time spent in remission before entry and the necessarily selected nature of the group (those with recently active but steroid-responsive disease) may be significant confounding factors.

Another multicentre study has specifically assessed the effect of budesonide 6 mg daily on endoscopic and symptomatic recurrence in the year following ileocolic resection (unpublished results). Disappointingly, no significant difference in recurrence was demonstrated overall at 1 year. The subgroup of patients operated on for 'disease activity', although somewhat ill defined as a group, showed a significantly lower endoscopic recurrence rate at 1 year compared with that in the placebo group (32 *versus* 65 per cent; $P = 0{\cdot}048$). The authors concluded that a role may exist for budesonide in patients resected for ileocaecal 'disease activity'. This implies that there may be a difference in the underlying disease processes generating 'fibrostenotic' and 'inflammatory' disease, and their susceptibility to steroid therapy; this is interesting in relation to the debate regarding 'types of disease'. Further work on the efficacy of budesonide is needed but, for now, it seems reasonable to suggest that any effect of budesonide is likely to require a dose of 6 mg or greater per day; it must be understood that benefit is presently unproven, even in patients rendered macroscopically disease free by resection.

Conclusion

The goal of reducing recurrence after surgery for Crohn's disease remains as pressing as ever. Despite further studies into risk factors for recurrence no clear clues exist relating to age, sex, site of disease or length of disease history. Data on the risks associated with smoking, particularly in females, have accumulated and it is appropriate to advise patients that smoking increases the risk not only of developing Crohn's disease but also of disease recurrence.

Endoscopic findings of early recurrence may predict later clinical recurrence and so offer the potential of an accurate early endpoint for clinical trials. The merit of dividing Crohn's disease into two clinical forms, referred to as 'stenosing/inflammatory' or 'obstructing/perforating', is still debated, but it may have significance both for studies of pathogenesis and for therapeutic trials.

Recent studies suggest that 5-ASA confers early benefit at doses between 2·4 and 3 g per day in patients undergoing ileocolic resection; the long-term role of this drug is uncertain. The oral steroid budesonide shows some promise in preventing the development of new lesions. Its side-effect profile makes it a candidate for further study but, as yet, there is no firm evidence of its worth in standard preventive management regimens.

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Review

Rational approach to combined carotid and ischaemic heart disease

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Background The management of patients with concomitant coronary and carotid artery disease remains a controversial subject. The aim of this review was to develop a rational plan for the management of such patients based on a review of the literature.

Method and results A retrospective review was carried out of relevant papers derived from the Medline database from 1964 to 1996.

Conclusion The management of patients with concomitant coronary and carotid artery disease has not yet been put to the test in a properly designed and randomized multicentre trial. It is suggested that, until the results of such a trial are available, the rational approach to combined symptomatic disease is combined carotid endarterectomy and coronary artery bypass grafting (CABG). Combined surgery is also appropriate for patients with symptomatic carotid artery disease and significant but asymptomatic cardiac disease. At present there is inadequate evidence to promote carotid endarterectomy for asymptomatic disease in combination with CABG.

Atherosclerosis results in localized plaque formation at preferential sites within the arterial tree, such as the carotid, coronary and lower extremity arteries. Patients presenting with symptomatic disease affecting one of these areas are likely to have manifest or occult disease in one or more of the other sites; management of such patients is complex and frequently ill understood.

It has been estimated that 2–18 per cent of patients having coronary artery bypass grafting (CABG) have severe concomitant carotid artery disease, although only a minority are symptomatic[1–7]. Conversely, up to 40 per cent of patients undergoing carotid endarterectomy have significant coronary artery disease[8]; myocardial events are the major cause of death in the immediate postoperative period in these patients. In this review the relationship between coronary and carotid artery disease is explored, and a rational approach is offered for the detection and management of patients with this complex dual pathology.

Risks of neurological events in patients undergoing coronary artery bypass grafting

CABG is one of the most commonly performed operations in the UK. As the associated mortality rate has fallen, concerns about morbidity have increased. Perioperative neurological events occur in 5 per cent of patients after CABG; these range from transient neurological events with no residual deficit at 30 days, to strokes with residual deficit (1 per cent)[9] and fatal brain injury (0·3 per cent)[10]. Although a good correlation has been demonstrated between carotid artery disease and neurological events during CABG, no study has convincingly shown that carotid artery disease is the cause of perioperative stroke. Neurological events following cardiac surgery are multifactorial in origin, and may be due to embolization of atherosclerotic debris from an atherosclerotic ascending aorta[11–13] or carotid artery[14–16], ventricular mural thrombi[4,6,17], or air, fat or platelet aggregates formed during cardiopulmonary bypass[6,17], or to cerebral hypoperfusion. Despite this, carotid artery disease is a strong risk factor for the development of postoperative stroke and the presence of such disease may be a marker for atherosclerotic disease elsewhere, such as a calcified aortic arch or intracranial disease.

The risk of developing a postoperative neurological event following cardiac surgery is 0–9 per cent in patients with a carotid artery stenosis of 50 per cent or greater[2,4,18–20]. In patients undergoing cardiac surgery, the prevalence of internal carotid artery stenosis greater than 50 per cent ranges from 3·8 to 18·7 per cent[2,4,5,19–21]. The lowest rate (3·8 per cent) was reported by Brener and colleagues[2] in a study of over 4000 male patients undergoing cardiac surgery. In this study, 9 per cent of patients with carotid artery disease had a neurological deficit in the postoperative period compared with 2 per cent without disease. The prevalence of carotid artery stenosis increases with age but, unfortunately, the age characteristics of the study population were not included in Brener *et al.*'s report. In a similar study by Faggioli and co-workers[4], the overall prevalence of carotid artery stenosis greater than 50 per cent was 18·7 per cent, with a 6·8 per cent prevalence of lesions of 75 per cent or more. The mean(s.d.) age of this study population was 63·5(9·2) years and severe carotid artery stenosis (greater than 75 per cent) occurs significantly more frequently in patients aged over 60 years (11·3 *versus* 3·8 per cent). Although the incidence of postoperative stroke increased with age, this increase was seen almost exclusively in older patients with carotid stenosis of 75 per cent or greater. These patients, all of whom were asymptomatic before surgery, had a postoperative stroke rate of 15 per cent. It is interesting to note that all initially woke following CABG surgery without a neurological deficit. A similar prevalence of carotid artery disease was reported by Berens and colleagues[5]. Of 1087 cardiac patients over 65 years old, 17 per cent had a carotid artery stenosis greater than 50 per cent and 5·9 per cent had a stenosis greater than 75 per cent Schwartz *et al*[21] also found that the risk of postoperative stroke increased with increasing severity of

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disease; 3·8 per cent of patients with a unilateral stenosis greater than 50 per cent suffered a hemispheric stroke, compared with 8·3 per cent of those with bilateral internal carotid artery stenosis of 80–99 per cent.

The presence of an asymptomatic internal carotid artery stenosis of 50 per cent or greater is associated with a mean annual ipsilateral stroke rate of only 2·8 (range 0·9–4·7) per cent[22–27]. For patients with an asymptomatic stenosis of 75 per cent or more, the mean annual risk of stroke is 3·6 (range 1·8–10·1) per cent[28–34], with only 75 per cent of strokes being ipsilateral to the stenotic artery. Three prospective randomized trials[35–37] designed to show the efficacy of prophylactic carotid endarterectomy in the treatment of patients with asymptomatic stenosis have failed to demonstrate that stroke or stroke-free survival is influenced by endarterectomy for asymptomatic carotid stenosis. However, the National Institute of Neurological Disorders and Stroke has recently issued a clinical advisory document stating that the Asymptomatic Carotid Atherosclerosis Study (ACAS), which includes more than 1500 patients, has been halted as it has shown a clear benefit in favour of surgery for patients with an asymptomatic carotid stenosis of 60 per cent or greater[38]. The European Asymptomatic Carotid Endarterectomy Study continues to recruit.

Risks of myocardial events in patients undergoing carotid endarterectomy

Approximately 50 per cent of patients with vascular disease have clinical evidence of coronary artery disease[39] and natural history studies have shown that ischaemic heart disease is the major cause of death in patients with asymptomatic carotid artery stenosis[40]. Data generated by the multicentre Coronary Arterial Surgical Study (CASS) have demonstrated that non-coronary surgery can be performed with relative safety in patients with coronary artery disease (2·4 per cent mortality rate and 1·1 per cent morbidity rate)[41]. However, patients requiring major vascular surgery are more likely to sustain a postoperative coronary event[42]. Using coronary arteriography to demonstrate coronary disease, Hertzer and colleagues[8] found coexisting coronary artery lesions in 93 per cent of patients undergoing carotid endarterectomy; coronary angiography disclosed lesions in 86 per cent of patients with no previous history of coronary artery disease, and these were significant in 40 per cent. Non-invasive cardiological screening including exercise electrocardiography (ECG), with or without exercise myocardial scintigraphy, in patients with symptomatic carotid artery lesions detects coronary artery disease in 24–41 per cent of those without a previous history of such disease[43–45].

The high prevalence of coronary artery disease accounts for the risk of coronary events being twice that of neurological events in patients undergoing carotid endarterectomy, yet detailed cardiovascular evaluation is rarely incorporated into the management of patients with cerebrovascular disease. Preoperative evaluation should be aimed at detecting both symptomatic and asymptomatic cardiac disease such that surgically correctable lesions are identified.

Patient assessment

Patients with simultaneous cardiac and carotid disease may present in three ways: with symptomatic cardiac disease and asymptomatic carotid disease, with symptomatic carotid disease and asymptomatic cardiac disease, and with symptomatic cardiac and carotid disease.

Symptomatic cardiac disease and asymptomatic carotid disease

A number of strategies, including altered anaesthetic and surgical technique to optimize cerebral blood flow, the use of cerebroprotective drugs[46,47], arterial line filters[48], membrane oxygenators[49] and resection of diseased aortic segments[14], has been developed to reduce the risk of stroke or neurological event during CABG. However, the preoperative assessment of patients undergoing cardiac surgery does not routinely include screening for carotid artery disease. Although symptomatic carotid artery stenosis may be detected by appropriate history taking or an asymptomatic bruit detected by auscultation, a significant number of patients with asymptomatic disease will be missed. If a mid-cervical bruit is audible, the likelihood of a stenosis being present is 64–85 per cent[50–54].

At present, duplex scanning is the method of choice in screening for suspected extracranial cerebrovascular disease[55,56]. It has replaced most of the indirect tests such as bruit analysis, oculoplethysmography and periorbital Doppler velocity studies, because both functional and anatomical information can be achieved in a single (duplex) study. Duplex scanning can detect a stenosis of the internal carotid artery with a sensitivity of 95 per cent, specificity of 94 per cent and positive predictive value of 91 per cent when compared with two-plane angiography[55]. However, there is a risk of assessing a high-grade stenosis as a total occlusion; this risk has been reported to range from 1 to 14 per cent[57–60].

In a recent review of duplex scanning in 142 vascular laboratories in the USA, the average cost of a single scan was US$181[61]. The cost in the UK would probably be less but, as the prevalence of carotid stenosis in patients undergoing CABG is less than 20 per cent, screening all patients undergoing cardiac surgery would be expensive. Therefore, screening should be confined to patients with established risk factors for developing perioperative stroke during CABG. These are advanced age[4,6,62,63], peripheral vascular disease[5,8] and cerebrovascular disease[3,4,6,8,63].

Symptomatic carotid disease and asymptomatic cardiac disease

In patients with carotid artery disease, risk stratification enables the identification of coronary artery disease and its severity; the likelihood of cardiac events can be predicted and appropriate pre-emptive measures can be taken before carotid endarterectomy. In a Veterans Administration study[64], 444 patients undergoing carotid endarterectomy were assessed for cardiac risk. Patients with a history of cardiac disease, defined as a history of CABG, angina, symptomatic myocardial infarction (MI), or evidence of an asymptomatic MI on ECG, had an increased incidence of perioperative myocardial events compared with those with no previous history of cardiac disease. There was no association between vascular risk factors and the risk of new cardiac events in patients with a history of cardiac disease. In contrast, patients without a history of cardiac disease had an increased risk of cardiac events if they had diabetes, peripheral vascular disease or intracranial occlusive disease (50 per cent or greater stenosis of the carotid siphon or middle cerebral artery on cerebral angiography). Patients with combinations of the three factors had the highest risk of cardiac events; only 13 per cent of patients with none of these factors had cardiac events, 36 per cent of those with one factor, 42 per cent with two factors, and 69 per cent with three factors.

Multivariate analyses of preoperative cardiac risk factors have been used to create various indices to predict cardiac events. The first of these was the Goldman index[65], which has been validated by a number of investigators[42,66–68], and a modified version has been described by Detsky and colleagues[66,67]. In a retrospective analysis of operative mortality and cardiac event rates in patients undergoing carotid endarterectomy, Musser *et al.*[69] reported an operative mortality rate of 1·1 per cent in patients in a low-risk group (Goldman index I and II), compared with 9·4 per cent in the high-risk group (Goldman index III and IV). Similar results were reported from the Cleveland Clinic 15 years ago; early mortality rate was 9·6 per cent in patients with clinically identifiable coronary artery disease *versus* 2·9 per cent in those free of coronary artery disease[70]. If we wish to report improved results in 15 years' time, patients with coronary artery disease must be identified before surgery and offered appropriate intervention.

Preoperative non-invasive cardiac assessment is of most value in patients at moderate risk of MI. If they have a good exercise tolerance, the risk of perioperative infarction is low[42,71,72]. However, exertion-related symptoms such as angina may be masked in the presence of lower limb vascular disease due to an inability to exercise. In such circumstances a low risk score does not rule out the presence of significant coronary artery disease[68,73,74]. Therefore, while a moderate or high risk index may be useful in predicting postoperative cardiac complications, a low score may not rule out the presence of coronary artery disease; additional tests are needed.

Exercise electrocardiographic stress testing This is a widely undertaken, incremental and well standardized investigation[75]. It is dependent on the patient's ability to exercise. In studies of patients undergoing major vascular surgery, 35 per cent were unable to achieve 75 per cent of their predicted maximal heart rate and had non-diagnostic electrocardiograms at the end of the stress test[75]. Using the exercise stress test, McPhail and colleagues[72] studied patients with peripheral vascular disease and abdominal aortic aneurysm. Despite using arm ergometry if the predicted maximal heart rate could not be achieved on a treadmill, only 30 per cent could reach 85 per cent of predicted maximal heart rate. Although those who reach 85 per cent of their predicted maximal heart rate and who maintain a negative stress test have a low probability of postoperative cardiac complications, too many do not achieve an exercise load sufficient to produce a meaningful result.

Preoperative electrocardiographic monitoring. Preoperative silent MI, as documented by ECG, has been reported to be useful in the prediction of cardiac complications after peripheral vascular surgery[73,76–78]. In a report from the Study of Perioperative Ischaemia Research Group, preoperative ischaemic changes identified patients who were at high cardiac risk; the probability of these patients developing a cardiac complication after operation was 33 per cent[79]. The absence of ischaemic events before or during operation did not rule out postoperative cardiac events and, in the subset of vascular patients, five of seven who suffered postoperative cardiac events had no preoperative ischaemia[80].

Myocardial perfusion imaging. The principle is that a radioactive tracer is used to study myocardial perfusion during maximal coronary vasodilatation. The usual perfusion tracers are ^{201}Tl, ^{99m}Tc–sestamibi (MIBI) and ^{99m}Tc-tetrofosmin. ^{201}Tl has been used clinically since the early 1970s for myocardial perfusion studies, whereas ^{99m}Tc–MIBI and ^{99m}Tc–tetrofosmin have been introduced more recently. Dipyrimadole-induced maximal coronary vasodilatation in combination with ^{201}Tl myocardial imaging has a sensitivity and specificity for the detection of coronary artery disease similar to those of exercise imaging[81], which it has largely replaced. The main advantage of the dipyrimadole test is that it does not require exercise or a target heart rate. It was initially assessed by Boucher *et al.*[82] in patients undergoing abdominal aortic aneurysm surgery or peripheral vascular reconstruction. Postoperative MI or myocardial death occurred in 8 per cent of patients, all of whom had ^{201}Tl redistribution on scanning. In contrast, none of those with persistent defects or normal scans had an ischaemic cardiac event. Subsequently, numerous reports have confirmed the ability of dipyrimadole–^{201}Tl redistribution, either alone or in combination with clinical characteristics, to identify patients at high risk of postoperative cardiac complications[73,83–94] These studies have been accused of selection bias and subsequent detection bias as, with few exceptions, patients were referred for evaluation and no attempt was made to conceal the results of the test from the investigators or physicians caring for the patient. In a recent study by Baron and colleagues[95], dipyrimadole–^{201}Tl scintigraphy did not appear to add important prognostic information for the prediction of serious cardiac complications.

Alternative coronary vasodilators include adenosine, a naturally occurring purine which mediates the cellular action of dipyrimadole and can be given intravenously for direct effect, and dobutamine, a β-agonist which increases myocardial oxygen demand through a combined inotropic and chronotropic action. Adenosine has been studied mainly for use with ^{201}Tl myocardial perfusion imaging and has been shown to compare well with exercise–^{201}Tl imaging[96–98]. Dobutamine has successfully been used for ^{201}Tl[99,100] and MIBI[101] myocardial perfusion imaging. It has also been used with ^{201}Tl imaging[102] to assess the risk of vascular surgery. There are few direct comparisons of the stress agents used in nuclear medicine studies but, in a comparison of adenosine and dobutamine for both MIBI single photon emission computed tomography and echocardiography, the two agents were found to be equivalent for MIBI scans[103].

Echocardiography. Myocardial perfusion imaging may be the best preoperative screening technique, but its availability is limited. Ventricular function is a strong predictor of operative and postoperative cardiac complications, and this may be assessed by echocardiography or ventriculography. M-mode echocardiography may be used to measure left ventricular dimensions, and two-dimensional echocardiography to assess global and regional function. When combined with anatomical detail and the assessment of valves with Doppler ultrasonography, useful information about left ventricular function can be provided. Stress echocardiography can predict cardiac complications, particularly if used to assess the development of abnormalities of wall motion induced by dobutamine[104].

Coronary angiography. Because the incidence of coronary disease in patients with carotid artery disease is so high, some authors have advocated coronary angiography in all[8]. This approach is not widely accepted and would result in considerable risk and expense. Preoperative coronary angiography should be performed only in patients who are considered at high risk of coronary events after non-invasive risk stratification[105].

Management of combined disease

Symptomatic cardiac and carotid disease

In many ways this is the easiest group to manage as there is little doubt but that both lesions require treatment. The difficulty is to decide whether the patient is best served by simultaneous or sequential operations. Unfortunately, the answer is not known.

The combined procedure was first proposed by Bernhard and colleagues[106] in 1972 and has found favour in a number of centres. The postoperative stroke rate of the combined procedure is reported to be 6 per cent, with an overall operative mortality rate of 6 per cent. In a meta-analysis of reports, the perioperative stroke rate was similar whether coronary and carotid surgery were carried out simultaneously or carotid surgery preceded coronary surgery, but the frequency of stroke was significantly greater if CABG preceded carotid surgery[38]. However, the frequency of MI and death was greater when carotid surgery preceded CABG.

Carotid endarterectomy may be performed before the institution of cardiopulmonary bypass or during bypass. Advocates of performing the endarterectomy first without cardiopulmonary bypass maintain that this ensures higher cerebral perfusion pressures during the operation, and subsequently allows for increased cerebral perfusion while on bypass. Initial endarterectomy is considered to be important because autoregulation of cerebral blood flow is lost distal to flow-limiting stenoses and cerebral blood flow then becomes pressure passive. Cardiopulmonary bypass can, however, be easily instituted should the patient become haemodynamically unstable. During the period of bypass the aim is to optimize cerebral perfusion in order to keep the perioperative stroke risk as low as possible. The perfusionist should maintain perfusion pressures in excess of 60 mmHg and avoid any hypotensive episodes. Pulsatile cardiopulmonary bypass should be used as non-pulsatile perfusion results in progressive systemic vasoconstriction which continues for some hours[107]. Tranmer *et al.*[108] reported significantly higher cerebral blood flow values under pulsatile flow conditions in experimental models. Systemic vasoconstriction is due to the release of vasoconstrictor substances including angiotensin II and vasopressin[91,93,109]. Vasoconstriction leads to increased left ventricular work and to reduced perfusion of viscera including the brain. Acid–base management during cardiopulmonary bypass is important and arterial partial pressure of carbon dioxide is one of the most significant determinants of cerebral blood flow[110]. The alpha-stat method of pH management is preferred because it is more physiological, by matching cerebral blood flow to metabolic demand[111].

Cardiopulmonary bypass is associated with the generation of microemboli. The repeated passage of the blood volume through the extracorporeal circuit results in contact activation of blood components. Synthetic materials which comprise the circuit as well as abnormal blood–gas interfaces are far removed from physiological endothelial cell contact. Contact activation in circulating blood leads to the initiation of the blood clotting cascade, complement activation, fibrinolytic mechanisms and kinin release[112]. As a consequence, leucocytes and platelets are activated and form microaggregates with erythrocytes and fibrin. Following formation, microaggregates pass in the circulation as microemboli, and lodge in the microcirculation of viscera. That such aggregates have been demonstrated in the retinal circulation[113] and in other areas is cause for concern. Although major cerebral embolic events are rare in association with cardiopulmonary bypass, the contribution of microemboli to more subtle forms of cerebral damage as manifested by neuropsychological deficit has yet to be determined. The microembolic load is minimized by using a membrane oxygenator which reduces the generation of microemboli reaching the cerebral circulation, compared with a bubble oxygenator[114]. Finally, an arterial filter is placed within the bypass circuit.

Transcranial Doppler ultrasonographic studies performed by Pugsley *et al.*[115] showed a marked reduction in microemboli reaching the brain when a 40-μm screen filter was placed in the arterial line. Advocates of performing the carotid endarterectomy on bypass maintain that systemic hypothermia (20°C) provides hypothermic cerebral protection during the period of carotid clamping and eliminates the need for a shunt[116]. Weiss and co-workers[116] cross-clamp the aorta before performing the endarterectomy as they are concerned about ventricular fibrillation while the heart is being cooled. Other workers do not cross-clamp, maintaining that ventricular fibrillation is safe at these temperatures[117]. The latter approach has the advantage that the period of aortic cross-clamping is limited to the interval necessary for the cardiac procedure, and any unexpected developments that prolong the non-cardiac portions of the combined procedure do not prolong aortic cross-clamping[118]. Alternatively profound hypothermia may be established by cooling with the perfusate. When cardiac ejection becomes ineffective, the aorta is cross-clamped and the patient is placed on cardiopulmonary bypass. Cooling continues until the nasopharyngeal temperatures become 13–15°C, and total circulatory arrest is established and carotid endarterectomy performed. Cardiopulmonary bypass is then re-established and the coronary operation proceeds as the temperature is slowly returned towards normothermia.

The recent publication by the American Heart Association of guidelines for carotid endarterectomy in patients with coronary artery disease concludes with an outline of indications under the headings: proven, acceptable but not proven, uncertain, and proven inappropriate[38]. For low-risk patients with a symptomatic carotid artery stenosis greater than 70 per cent who require CABG for myocardial disease, carotid endarterectomy performed by a surgeon whose combined surgical mortality and morbidity rate is less than 6 per cent is considered by this report to be 'acceptable but not proven' when performed synchronously with CABG. An uncertain indication is transient ischaemic attacks in a patient with carotid artery stenosis of less than 70 per cent who also requires CABG.

Carotid angioplasty has recently been introduced and is presently being compared with carotid endarterectomy. If it proves successful in the management of symptomatic carotid artery disease without an increase in associated strokes, it would offer an alternative method of managing symptomatic carotid artery disease before coronary surgery.

Symptomatic cardiac disease and asymptomatic carotid disease

The role of carotid endarterectomy in patients with symptomatic myocardial disease and asymptomatic carotid stenosis greater than 70 per cent has not been evaluated fully. Such patients have a higher incidence of postoperative stroke than those without carotid disease but, as yet, there are no proven indications for a combined procedure and the role of such surgery is 'uncertain'. The optimal strategy for the management of these patients will be established only by a well designed randomized controlled trial. However, it must be remembered that for patients with asymptomatic carotid artery disease and no ischaemic heart disease the National Institute of Neurological Disorders and Stroke has halted the ACAS because of a clear benefit in favour of surgery for patients with carotid stenosis greater than 60 per cent.

Symptomatic carotid disease and asymptomatic myocardial disease

If significant myocardial disease is detected before surgery, measures can be taken to improve the cardiac status by pharmacological manipulation. Such patients may also benefit from risk-reducing interventions such as invasive peroperative monitoring. Alternatively, if a correctable lesion is found, the cardiac status may be improved before surgery by angioplasty. If main stem or triple vessel disease is identified, the patient should be considered for the combined operation.

Conclusion

Although some 2–18 per cent of patients undergoing CABG have severe concomitant carotid artery disease, only a small proportion is symptomatic. However, CABG is fast becoming one of the most frequently performed operations and the selection criteria for such surgery have been widened, with older patients being accepted. The incidence of carotid artery disease increases with age, as does the risk of perioperative stroke. So should all patients be screened for carotid artery disease? This would add to the cost of CABG and potentially delay surgery. A selective policy, screening those over 60 years old or who have peripheral vascular disease or a history of cerebrovascular disease, would detect a significantly higher incidence of disease and would be cost effective.

The management of patients with concomitant symptomatic coronary and carotid artery disease is controversial. Two large multicentre studies[119,120] have shown a significant reduction in the long-term risk of stroke after surgery for symptomatic carotid artery disease, and similar results are expected from ongoing trials for asymptomatic disease. Nevertheless, the management of combined disease has not yet been put to the test in a properly designed and randomized multicentre trial. However, a meta-analysis of reports on the management of concomitant symptomatic carotid and coronary artery disease has failed to show that the combined procedure is associated with a greater risk[39] and it has in its favour an economic argument. Daily and colleagues[121] have shown it to be cost effective, with a saving of 25–30 per cent compared with a staged surgical approach, and with no increase in the permanent stroke or death rate. Until the results of a properly designed and randomized multicentre trial became available, the rational approach to concomitant symptomatic coronary and carotid disease appears to be combined carotid endarterectomy and CABG.

The management of asymptomatic carotid disease in the presence of symptomatic cardiac disease is more controversial. There is evidence that carotid endarterectomy reduces the incidence of ipsilateral carotid artery territory ischaemic stroke in patients with a severe asymptomatic carotid stenosis. Such patients have a reduced risk of surgery-related stroke or death compared with those with symptomatic disease undergoing endarterectomy[122]. It is not known whether this holds true in the presence of combined coronary and carotid disease or during a combined procedure. Once again, this illustrates the need for a properly designed and randomized trial.

Finally, patients with symptomatic carotid artery disease and significant but asymptomatic cardiac disease have a significant cardiac-related mortality during carotid endarterectomy alone[123]. All preoperative measures should be taken to identify those at risk. If a surgically treatable cardiac lesion is identified, management should be as for combined symptomatic coronary and carotid disease.

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Review

Monoclonal antibody treatment of colorectal cancer

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Background The recent development of adjuvant monoclonal antibody immunotherapy for patients suffering from colorectal cancer has led to a re-evaluation of the role of these molecules in the treatment of solid tumours. In particular, interest has been directed at identifying appropriate candidates for therapy, evaluating treatment schedules and developing new molecules of therapeutic potential.

Methods This is a review of published data on patients undergoing antibody therapy. In addition, current theories of the mechanism of action of antitumour monoclonal antibodies are presented, along with potential future therapeutic approaches.

Results and conclusion Monoclonal antibody-based adjuvant therapy of colorectal cancer appears to be effective; international multicentre trials continue. The development of new molecules, such as chimaeric antibodies, offers the potential of increased tumour targeting with reduced toxicity. Such molecules may be used alone or in combination with agents such as chemotherapy or cytokines.

When monoclonal antibodies were first produced by Kohler and Milstein[1] in 1975 it was thought that they would revolutionize both laboratory and clinical immunology. For the first time, technology was able to produce a large amount of antibody specific for a single antigen. These novel molecules were hailed as 'magic bullets' which might target diseased cells, especially malignant cells, and become the anticancer agents of the future. Their use in the laboratory is unquestioned, radioimmunoassay, enzyme-linked immunosorbent assay and flow cytometry are just some of the techniques that rely on monoclonal antibodies to label specific molecules. However, the performance of monoclonal antibodies in clinical practice (especially as chemotherapeutic agents) has not been so successful. With an emphasis on colorectal cancer and the 17-1A antibody, this review considers the evolution of monoclonal antibodies as antitumour agents from their initial use in advanced disease to the recent exciting results from their use as adjuvant therapy.

Malignant disease is the ideal candidate for treatment with monoclonal antibodies. *In vivo*, the immune system acts to reject the cancer cell in a variety of ways, such as antibody-dependent cell-mediated cytotoxicity (ADCC), complement-dependent cytotoxicity, lysis by killer and natural killer cells, and T cell-mediated immunity. Monoclonal antibodies kill cancer cells *in vitro* by ADCC[2–4] and it was thought that administration of these molecules *in vivo* would harness the host immune defence system to bring about tumour cell death. ADCC occurs when the Fc end of the monoclonal antibody attaches to an Fc receptor on an effector cell, either a monocyte–macrophage or a natural killer cell, and the Fab end of the molecule attaches to a tumour-specific antigen on a tumour cell. By cross-linking the two cells the effector cell brings about tumour cell lysis[5,6].

Monoclonal antibodies can be directed against tumour-associated antigens (TAAs) which exist on a wide variety of tumour cells. The ideal TAA is one that is expressed exclusively or in a higher proportion on tumour cells than on normal cells. This allows the tumour cell to be identified selectively by the antibody. To date, many TAAs have been identified[7–11]. Some are shed from the cell surface and act as tumour markers which can be measured in the blood, for example carcinoembryonic antigen[12,13]. Other antigens are not shed and so can usefully be targeted by monoclonal antibodies *in vivo*.

One of the most well known TAAs is 17-1A. It is highly expressed on tumours of epithelial origin, such as colorectal cancer and most other gastrointestinal malignancies[14–16]. The antigen is not shed from the cell membrane and is not detectable in serum[17]. However, it is not completely tumour specific as it is also expressed, although in much smaller amounts, on normal colonic mucosa[18,19]. A murine monoclonal antibody, m17-1A, directed against this antigen is the molecule that has been used most widely in clinical trials, usually in patients with colorectal carcinoma.

Principles of immunotherapy

Solid malignancies kill by metastasizing[20] and for most, especially colorectal cancer, the mainstay of treatment is still surgery[21]. There is a real need to develop new therapies for colorectal cancer as it is one of the commonest malignancies in Western society[22] and its associated mortality rate has not changed appreciably over the past 40 years[23], despite screening programmes and advances in surgical treatment[24,25].

Unfortunately, at the time of surgery occult metastases are often present and these cells remain after treatment[26]. Metastatic cells have been identified in the peritoneal cavity[27] at the time of surgery and in the bone marrow of patients during the early occult stages of tumour spread[28]. For colorectal cancer, disseminated epithelial tumour cells can serve as independent and strong predictors of later clinical relapse[29]. This has led to the concept of adjuvant therapy aimed at targeting residual micrometastatic disease in the early postoperative period when the tumour

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load is small. The place of adjuvant treatment after surgery is well recognized[30]; adjuvant 5-fluorouracil chemotherapy has been demonstrated to be of therapeutic benefit in colorectal cancer[31]. However, this approach is non-specific and the cytotoxicity profile is related directly to the effect on normal cells. Monoclonal antibodies, on the other hand, should be more specific and target micrometastatic disease selectively. In addition, most micrometastatic cells appear to be cycling or dormant[32,33] and so tend to be resistant to antiproliferative chemotherapeutic agents, whereas monoclonal antibodies act independently of the cell cycle. The need for more effective treatments to combat colorectal cancer coupled with the 17-1A antigen, which is highly expressed on such cancer cells, has meant that colorectal cancer is one of the solid malignancies most frequently studied for its response to monoclonal antibody treatment. Unfortunately, initial studies involved patients with advanced disease and it is only in recent times that monoclonal antibodies have been used as adjuvant treatment.

Monoclonal antibodies and cancer

Monoclonal antibodies have several uses in the clinical management of malignant disease. They may be radiolabelled and used as tools in diagnostic radiology to identify sites of malignancy, either before[34] or during[35] operation. They may be harnessed to drugs or toxins[36], or the native molecule may be used alone[37,38]. Radiolabelled monoclonal antibodies have been used to detect colorectal cancer and B72.3 directed against glycoprotein-72 (TAG-72) antigen and labelled with indium-111 has been subjected to several large studies. Although not 100 per cent specific, over 80 per cent of tumours were detected, leading to a change in management in 25 per cent of patients[39,40]. Such techniques may complement conventional radiology and may help when tumour markers indicate disease progression but no abnormality is detected on computed tomography, or where lymph nodes detected on scanning may be either malignant or reactive. Monoclonal antibodies may also be used as tumour-directed carriers for cytotoxic drugs or radioisotopes; clinical trials have shown some antitumour activity in several forms of malignancy including melanoma[36] and colorectal carcinoma[41].

Monoclonal antibody treatment using the native molecule

The main bulk of clinical trials has used native monoclonal antibodies as anticancer agents. The concept of such immunotherapy for cancer is not new[42]. As early as 1927, Lindstrom[43] used antisera to treat leukaemia, and in 1953 Pressman and Korngald[44] used radiolabelled polyclonal antibodies to detect osteogenic sarcoma *in vivo*. Initially, animals were immunized with cancer cells and their serum was used for therapy, but this was problematic owing to the side-effects of the heterogeneous antibody response. On the other hand, monoclonal antibodies have been used to treat a wide variety of solid and haematological malignancies and have, in general, been well tolerated[45–47]. Side-effects are usually relatively minor, ranging from fever, urticaria and malaise[48–50] to anaphylaxis[50,51]. These allergic reactions are a result of the immune response to the administration of a foreign protein. Almost all trials to date have used murine monoclonal antibodies which stimulate the immune system to produce human antimouse antibody (HAMA). HAMA is detectable in the circulation approximately 10–30 days after administration of the monoclonal agent[46,52,53]. In most trials, allergic responses could be predicted accurately by a skin prick test[54].

Clinical response has been variable and somewhat disappointing. Patients with leukaemia have had transient reductions in the numbers of leukaemic cells[48], and there have been occasional responses in patients with melanoma and neuroblastoma[49,50]. In general, antibody therapy has more often induced remission in patients with lymphoma or leukaemia[55] than in those with solid tumours[56]. Using m17-1A, many studies have demonstrated occasional objective partial and complete responses in patients with colorectal cancer[45,47,51,57,58] but no consistent pattern of response or improvement in survival has been found. Many trials have been performed over the 20-year period since monoclonal antibodies were introduced, almost exclusively on patients with advanced disease. Continuing depressing results after the initial excitement of monoclonal antibody production led to these agents falling in popularity.

A recent study by Reithmuller *et al.*[59] has renewed enthusiasm for monoclonal antibody treatment by demonstrating success with m17-1A as adjuvant therapy for colorectal cancer. This makes immunological and pharmacological sense, as the micrometastatic cells that remain after surgery occupy an unshielded position in mesenchymal tissue and constitute a small tumour load. This is more easily targeted by a monoclonal antibody than the large tumour burden present in patients with overt metastatic disease. One hundred and eighty-nine patients who had undergone surgery for Dukes C adenocarcinoma of the colon were randomized to management by observation or m17-1A. Patients received 500 mg m17-1A followed by 100-mg infusions at intervals of 1 month for 4 months. The antibody was well tolerated. After a median follow-up of 5 years, m17-1A treatment was found to reduce the overall mortality rate by 30 per cent and the recurrence rate by 27 per cent. Patients in the m17-1A arm of the trial had more local recurrences and fewer distant metastases than those in the control group. This supports the theory that antibodies are most effective against individually dispersed cells, such as micrometastases, and less effective against local tumour nodules or aggregates of cells. The authors concluded that m17-1A treatment could prolong life and remission periods in patients with Dukes C colorectal cancer[59]. While recognizing that this is only a single study, it is encouraging that after so many disappointing trials in patients with advanced cancer, the principle of adjuvant therapy with monoclonal antibodies has at last been supported. At present there is an ongoing large international multicentre randomized controlled trial attempting to confirm these initial data. In addition, this large trial includes a third arm addressing the potential additional benefit of combination therapy (with conventional chemotherapy) in view of the theoretical advantages of combining two independent and non-competing mechanisms of cellular cytotoxicity.

Are there better molecules?

Although the therapeutic effects of murine monoclonal antibodies such as m17-1A have only just been demonstrated, monoclonal antibody technology has advanced such that these murine molecules may no longer be the most effective available molecules for the job. Murine monoclonal antibodies have a modest biological activity, a short circulating half-life and, as previously outlined, their administration induces a HAMA response. Genetic technology has allowed the hybridization of antibodies to produce 'chimaeric' antibodies which have the variable antigen-binding region of a mouse monoclonal antibody, but with a human constant region. This gives the molecule the antigen-binding specificity of the murine monoclonal whereas the human part imparts a longer half-life, and makes it less immunogenic and more easily tolerated by the host immune defence system[60,61].

A chimaeric form of the 17-1A antibody has been produced which has similar patterns of reactivity with colonic cancer and other tissues to those of the murine molecule, and is able to mediate ADCC in a 4-h chromium release assay[62].

In some studies, chimaeric antibodies have been found to mediate cell-mediated cytotoxicity more effectively than their murine counterparts[63–66]. This has been demonstrated for the chimaeric version of the 17-1A antibody by the present authors and others against human colorectal cancer cells[67,68]. *In vivo*, a phase I trial with chimaeric 17-1A showed it was well tolerated by patients with metastatic colorectal cancer, with no allergic or toxic reactions. As predicted, the chimaeric antibody had sixfold longer circulation time than the murine molecule and was less immunogenic in that only one in ten recipients developed a low antibody titre against the murine variable domain[67]. It may be, therefore, that chimaeric 17-1A should be the next in line for testing in an adjuvant trial; it may not only be more beneficial to the patient, it may also be a more efficient anticancer agent.

However, there is an argument that the immune response triggered by murine monoclonal antibodies may actually be of benefit in terms of antitumour activity through the production of anti-idiotypic antibodies. The anti-idiotypic response was first described by Jerne[69] and is based on the fact that an antibody's variable regions may act as antigenic determinants which generate a network of interacting antibody molecules and lymphocytes in the immune system. Within this set of anti-idiotypic antibodies will be antibodies directed against the antigen-binding site of the antibody and these will be internal images of the antigen (*Fig. 1*). Such antibodies may continue to act as a stimulus for the immune response after the initial monoclonal antibody had been cleared from the circulation, thereby generating long-term immunity against tumours. There is some evidence that patients who show an anti-idiotypic response have a more successful clinical outcome[57,70–72], but other studies have not supported this[73–75]. Certainly, in the study by Reithmuller *et al.*[59], although 80 per cent of the patients who received m17-1A developed a HAMA response, analysis showed that there was no difference in HAMA titres between those who responded to m17-1A and those who did not. As chimaeric molecules are less immunogenic, if part of the anticancer effect is indeed by anti-idiotypic response, they may actually be less effective in bringing about tumour cell lysis *in vivo*. However, the murine end of the molecule is still present, suggesting that the idiotypic response is still possible with the chimaeric antibody, and this was shown to occur when c17-1A was used in clinical trial[67]. What is now needed is a clinical trial comparing a chimaeric and murine monoclonal antibody directed against the same TAA. This should not only allow comparison of the two molecules as antitumour agents, but also give some insight into the dominant mechanism of action of a monoclonal antibody directed against a TAA.

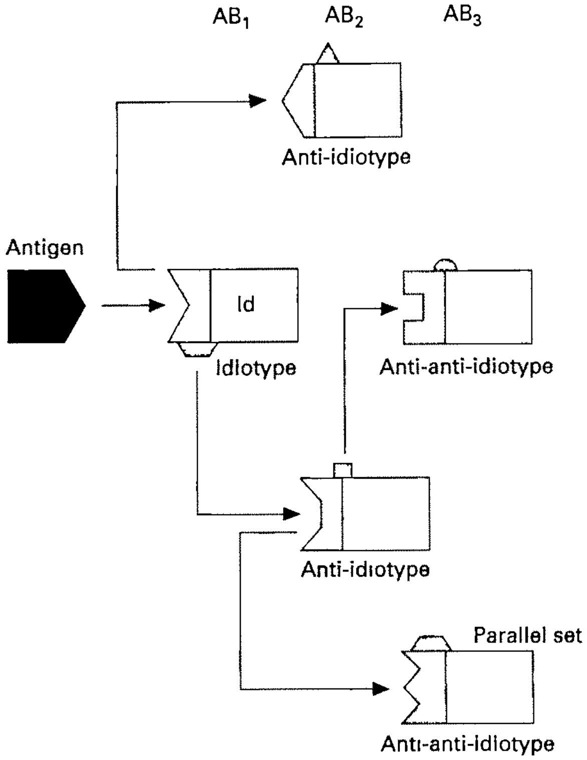

Fig. 1 Diagrammatic representation of the generation of anti-idiotypic (AB$_2$) and anti-anti-idiotypic (AB$_3$) antibodies. Id, idiotype

Results of immunotherapy can improve only as more efficient antibodies and more specific tumour antigens become available. Monoclonal antibody 323/A3 is an antibody directed against the 17-1A antigen which binds to a different epitope than the 17-1A antibodies. A comparative study of the chimaeric forms of 17-1A and 323/A3 antibodies demonstrated a higher affinity of the 323/A3 antibody for its antigen, more efficient complement-dependent killing and superior ADCC than the 17-1A antibody. There was also increased expression of the 323/A3 epitope on colorectal cancer cells compared with the 17-1A antigen[76]. Likewise, GA733 is an antibody directed against an epitope of the 17-1A antigen which has been shown to have enhanced cytotoxicity compared with m17-1A *in vitro* and in tumour-xenografted nude mice[6,77]. Native antibody[78] and Ab2[79] preparations of GA733 have been administered to patients in phase I studies. The higher affinity of these antibodies and their enhanced cytotoxicity in comparison to 17-1A may make them more effective anticancer agents. Combinations of antibodies directed against different epitopes of the same antigen may also prove useful[80].

More specific antibodies may also prove more effective in clinical practice; 17-1A, although present on the colorectal cancer cell, is also expressed on normal tissues[18,19] and so is not strictly a tumour-specific antigen The antigen SF25, on the other hand, although expressed in high density on colorectal tumours, is not present on normal colonic mucosa and is more specific for the cancer cell[81–83]. Furthermore, the present authors have shown that a chimaeric antibody cSF25 directed against this antigen is a more effective mediator of ADCC against colorectal cancer cells than either murine or chimaeric 17-1A[68–84]. If the results of Reithmuller *et al.*[59] are borne out in future studies, the use of more efficient and more specific antitumour monoclonal antibodies may lead to even more impressive results for adjuvant therapy.

Other options for immunotherapy

Other options for the immunological manipulation of the cancer response include bispecific antibodies and cancer vaccines. Advances in hybridoma technology and molecular biology have made possible the design of novel antibody-based constructs, such as heteroconjugated antibodies involving the linkage of two distinct monoclonal antibodies at the Fc receptor level using a chelating agent. Cross-linking an antitumour antibody, specific for tumour cell surface antigens, and an antilymphocyte antibody, specific for the T cell receptor complex CD3, produces a heteroconjugate that can redirect T cells to lyse tumour cells. Such conjugates are cytolytic to colonic cancer cells *in vitro* and in animal models[85]; one has been produced against 17-1A[86]. They are also able to augment tumour-infiltrating lymphocyte-mediated cellular cytotoxicity[87,88]. Bispecific antibodies that interact with tumour and effector targets via Fab domains may improve effector–target interactions *in vivo*: the interaction of these antibodies with effector cell Fc receptors, in contrast to antibodies with conventional structure, is not competitively inhibited by human immunoglobulin[89,90].

Cancer vaccines that harness the T cell response are also a possible mode of treatment[91,92]. The antitumour response to the vaccine is complex and probably also involves ADCC by both monocytes and natural killer cells, anti-idiotype production and complement binding[93]. Whole cell tumour vaccines used to treat cancer to date consist of either irradiated autologous or allogeneic tumour cells, usually coinjected with an adjuvant such as bacille Calmette–Guérin (BCG). Gene transfer, whereby the genetic material of a cell is altered to produce a new cellular phenotype, also holds promise in the production of vaccines. Gene transfer to effector cells may enhance their cytokine expression. Alternatively, tumour cells may be manipulated to increase TAAs, increase major histocompatibility complex expression or induce release of local cytokines[94]. Gene transfer techniques are being considered as a treatment for genetic disease and, theoretically, such therapy may be able to 'switch off' oncogenes or replace tumour suppressor genes. However, the complex techniques required mean that, in practice, this remains speculation.

The ultimate goal of tumour vaccine design is the generation of antigen-specific vaccines which obviate the need for the individual's own tumour cells as the source of antigen. Anti-idiotypic antibodies (AB_2) have potential as antitumour vaccines as they act as an idiotypic replica of the antigen and stimulate cellular responses. When administered to patients, AB_2 generates cellular immune responses, such as interleukin (IL) 2 production in the serum, and increases lymphocyte proliferation[95]. Now that monoclonal antibodies are beginning to fulfil their promise as an effective treatment for cancer, these other therapeutic immunological options may also become reality.

Augmentation of antibody therapy

The effects of monoclonal antibodies may be enhanced by immune modulators such as cytokines. IL-2[96–98], IL-1[99], tumour necrosis factor (TNF) α[100] and interferon (IFN) γ[100,101] have been shown to enhance ADCC *in vitro*. Several studies have also used the cytokines IFN-γ[102–104] and granulocyte–macrophage colony-stimulating factor[105,106] to enhance the effects of monoclonal antibodies *in vivo*. Despite enhancing cellular mechanisms of antitumour activity, use of these cytokines did not produce much improvement in clinical response. However, once again these studies were performed in patients with advanced disease. The present authors have shown that monoclonal antibodies which have superior antitumour effects may bring about more cytokine release than their less cytolytic counterparts[84]. cSF25, an extremely effective antibody against colorectal cancer, produced more IL-1β and TNF-α than either c17-1A or m17-1A. Furthermore, both chimaeric antibodies brought about more cytokine release than murine 17-1A. Whether the cytokine release is responsible for the superior tumour lysis is not proven, but there is no doubt that cytokines and monoclonal antibodies are inextricably linked in the immunological response to cancer. As understanding of this process evolves, augmentation of therapies with cytokines may also become a real option in treatment.

Conclusion

It is 20 years since monoclonal antibodies were first produced. Over this period, small trials in patients with advanced malignancy have not fulfilled the potential of these molecules as antitumour agents. Throughout its history, tumour immunology has been characterized by recurrent cycles of optimism and enthusiasm followed by disappointment and disillusionment. Recent evidence in patients with smaller tumour loads suggests that monoclonal antibodies may increase survival in those with colorectal cancer. Over the same timespan, the development of cancer-specific antibodies and chimaeric antibodies has provided molecules waiting to be tested that may be more effective *in vivo* than m17-1A. Reithmuller *et al.*, in their paper[59] reporting the exciting results of therapy with m17-1A, stated 'it is somewhat ironic that a monoclonal antibody which does not distinguish malignant from normal epithelial cells, is among the first to convey a survival benefit for cancer patients'. More results from the m17-1A trial, and from trials using newer and more specific antibodies, are eagerly awaited. The era of structurally defined tumour antigens and more specific antibodies should allow the opportunity to understand whether the sustained optimism of tumour immunologists has been justified. Rumours of the demise of the monoclonal antibody as a treatment for cancer may well have been exaggerated.

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Digest

Dr Keizo Sugimachi, Editor-in-Chief of *Surgery Today* (*The Japanese Journal of Surgery*), has selected from the January to June 1997 issues of his journal for this 6-monthly digest. A digest of *BJS* for the same period written by Mr Colin Johnson, European Editor, appears in the Japanese journal.

Surgery in elderly patients

Postoperative delirium is a common complication which can interfere with the surgical treatment and recovery of elderly patients, and is likely to prolong their hospitalization[1]. Unfortunately, there is as yet no completely effective preoperative and/or postoperative technique of patient care to reduce or prevent postoperative delirium. In this study 36 patients, aged over 70 years undergoing gastrointestinal operations, were assessed to examine the relationships between the preoperative cognitive state, the postoperative sleep cycle and the occurrence of postoperative delirium. All patients were evaluated before operation using the revised version of Hasegawa's dementia scale (HDS-R). The authors correlated these test results and assessed the sleep-wakefulness disturbance after operation, to obtain a clinical Diagnostic and Statistical Manual of Mental Disease (DMS)-III diagnosis of postoperative delirium. Postoperative delirium occurred in six of 36 patients. The patients who developed postoperative delirium demonstrated preoperative cognitive impairment, and had a short sleep period during the night and a long sleep period during the day. After operation, these results suggest that HDS-R is a useful method of evaluating preoperative cognition in elderly patients. Considering that sleep deficiency is likely to predispose elderly patients to postoperative delirium, techniques to prevent sleep deprivation may be of considerable value in minimizing the incidence of postoperative delirium.

A total of 828 patients with oesophageal cancer was treated at the Second Department of Surgery of Tokai University in the 20-year period from 1975 to June 1994, including 45 patients over 80 years old[2]. The authors reviewed these elderly patients to assess the optimum therapeutic approach for such individuals. In recent years, the number of elderly patients with oesophageal cancer has steadily increased. Advanced cancer is more common among this group, but early cancer has also been detected more frequently in recent years. Of the 45 elderly patients in the series, 36 were encountered in the last 10 years. As 13 of the patients had multiple cancers, a careful work-up was necessary before operation. Since most patients (40) had complications and were also in a poor general condition, limited surgery was recommended in consideration of the postoperative quality of life. It may be possible to extend the indications for endoscopic mucosal resection to submucosal, cancer without lymph node swelling. Postoperative complications occurred in 60 per cent of those undergoing surgical resection or oesophageal bypass, although there was only one death. The 5-year survival rate after surgical resection was 31 per cent. These results therefore support the use of surgical treatment for selected elderly patients with oesophageal cancer.

Carcinoma of the oesophagus

To define the rational extent of dissection in radical oesophagectomy for oesophageal cancer, survival was studied according to nodal status in 154 patients undergoing extended radical oesophagectomy[3]. The incidence of cervical metastasis in patients with upper or middle oesophageal tumours did not differ between those with favourable (grade N (where N = number of positive nodes) 4 or less) ($n = 42$) or unfavourable (grade N 5 or more) ($n = 15$) lymph node status, at 29 and 20 per cent respectively. On the other hand, in patients with lower oesophageal tumours, the incidence of cervical metastasis was significantly lower in those with favourable grade (grade N 4 or less) node status than in those with unfavourable grade (grade N 5 or more) node status, at 6 and 47 per cent respectively. Survival did not differ in patients with upper or middle oesophageal tumours according to whether they had regional ($n = 42$) or distant ($n = 15$) lymph node metastases, the 5-year survival rates being 12 and 25 per cent respectively. However, in patients with lower oesophageal tumours, none of 10 patients with distant node metastases survived for more than 4 years, whereas the survival rate was 44 per cent at 5 years for 36 patients with regional node metastases. These results show that cervical lymphadenectomy should only be performed as part of radical oesophagectomy in those patients with upper or middle oesophageal cancer.

For immunohistochemical investigation and clarification of the relationship between the vascular volume in oesophageal carcinoma and the proliferative activity of its tumour cells, surgical specimens of squamous cell carcinoma (SCC) of the oesophagus from 15 patients were examined[4]. The vascular volume was evaluated by immunostaining for platelet–endothelial cell adhesion molecule-1 with monoclonal antibody JC70, and the proliferative activity of the carcinoma cells was evaluated by immunostaining for proliferating cell nuclear antigen (PCNA) with antibody 19A2. The ratio of the vascular area to the tumour area and the labelling index (LI) for PCNA in the carcinoma cells was then calculated. The antibody JC70 was used for detecting blood microvessels in oesophageal carcinoma immunohistochemically. The vascular volume, expressed as the ratio mentioned above, was higher in well and moderately differentiated SCCs than in poorly differentiated SCC ($P<0{\cdot}01$), and the PCNA LI did not depend on the degree of differentiation. However, there was a significant inverse relationship between the ratio of the vascular area to that of carcinoma and the PCNA LI of the carcinoma cells ($P<0{\cdot}01$). These findings show that angiogenesis is greater in oesophageal carcinomas with little proliferative activity.

Carcinoma of the colon and the rectum

Hepatic metastasis of colon cancer is an important prognostic factor for survival. In this study, the authors examined the effect of gene therapy using the herpes simplex virus thymidine kinase (*HS-tk*) gene with short-course ganciclovir (GCV) treatment for multiple hepatic metastases of murine colon cancer[5]. Colon 26 cells transfected with the *HS-tk* gene were found to be sensitive to GCV in a concentration-dependent way. On the other hand, induction of the *HS-tk* gene in the cells had no influence on cell growth *in vitro*. However, multiple hepatic metastases of Colon 26 cells transfected with the *HS-tk* gene were significantly suppressed by GCV treatment. These results suggest that *HS-tk* gene therapy is useful for the treatment of hepatic metastasis in colon cancer.

A review was conducted to evaluate the current status of rectal carcinoids from multiple systemic aspects, based on extensive information provided by 1271 cases cited in 465 international articles published since 1912[6]. Each case report was read carefully, computerized and analysed by the gut–pancreatic endocrinoma analysis system (Niigata Registry). To avoid duplication, cases without individual identification, such as the age and sex of the patient, and those with identical clinical and laboratory data and institutes of source, were excluded. Where appropriate, selected cases from an overall gastrointestinal series consisting of 4461 cases similarly documented in the same registry were referred for comparison. The representative characteristics of rectal carcinoids consisted of a male preponderance, small tumours of 10 mm or less at detection, predominant submucosal invasion with a relatively high incidence of metastases, a high incidence of haematogenous spread, a predominant histology of the B-type growth pattern, a low rate of silver reactivity, the infrequent association of carcinoid syndrome, and relatively high mortality rate within 5 years after removal of the lesions.

Breast cancer

A study was conducted to analyse retrospectively the results of performing sector resection on 56 breasts in 54 patients with breast cancer[7]. The glands were resected with a 2-cm tumour-free margin on both lateral sides and the distal side, and with more than a 3-cm tumour-free margin on the nipple side. The frequency of positive resection margins for the cancer cells was seven of 56 (12 per cent) on the nipple side and 12 of 46 on the lateral sides, with an overall frequency of 15 of 56 (27 per cent). There were positive resected margins for cancer cells on both the nipple and lateral sides in four of 46 patients. Assuming the equivocal margins were positive for cancer cells, an accurate diagnosis by frozen-section examination was made in 51 of the 56 operations (91 per cent). Additional resection of the margins was performed in all 20 cases in which there was a positive resected margin for cancer cells according to the diagnosis by frozen section. Thereafter, the resected margins became negative in 13 cases, but remained positive in seven. These results show that performing diagnosis by frozen section of the surgical margins is an effective guide to adequate tumour resection.

The effect of age on the prognosis of breast cancer remains controversial. To investigate the role of age, Tsuchiya *et al.*[8] reviewed 316 patients with stage I or II breast cancer. There were 14 patients below 34, 146 between 35 and 49, 115 between 50 and 65, and 41 over 66 years of age. No correlations were observed between age and clinicopathological variables. Patients aged 34 years or less with breast cancer had a significantly worse survival rate than those in the older age groups. Multivariate analysis also showed younger age to be a significant factor, followed by lymph node status. Therefore, younger age at onset is considered to be an independent prognostic factor.

Endoscopic surgery

To evaluate the benefits of performing laparoscopic cholecystectomy in patients with cirrhosis, data on 13 patients with liver cirrhosis who underwent cholecystectomy for gallstones between 1989 and 1995 were collected retrospectively from charts filed at Fukuoka City Hospital[9]. These 13 patients were classified into two groups; one comprised seven patients who underwent laparoscopic cholecystectomy and another comprised six who underwent open cholecystectomy. No statistical differences were observed in the duration of operation or intraoperative blood loss between the two groups; however, the serum C-reactive protein level was significantly higher in the open cholecystectomy group than in the laparoscopic cholecystectomy group. Laparoscopic cholecystectomy was followed by a significantly earlier resumption of a normal diet ($P<0{\cdot}05$) and a shorter hospital stay ($P<0{\cdot}05$) in comparison to the open procedure. All of the patients who underwent open cholecystectomy had an uneventful clinical course; however, one of those who underwent laparoscopic cholecystectomy suffered from intractable ascites after operation. The difference in the cost of hospitalization between the two groups was not statistically significant. These findings suggest that the therapeutic significance of performing laparoscopic cholecystectomy in patients with cirrhosis should be assessed after carefully evaluating all factors including mortality and morbidity rates, and cost-effectiveness. Thus, further controlled trials are necessary.

Tsuboi *et al.*[10] describe a technique for closure of a patent ductus arteriosus (PDA) using a method of video-assisted thoracoscopic surgery derived from video-assisted endoscopic surgery. This technique was performed on five patients with a mean age of 3 years and a mean weight of 13·7 kg during 1994 and 1995. Under general anaesthesia, two 10-mm cannulas and two or three 5-mm cannulas were inserted through the left thoracic wall. A video camera and specially designed surgical tools including scissors, dissectors and a clip applicator were then introduced. The ductus was dissected, and two titanium clips were applied to interrupt the ductus completely. Successful closure of the PDA by this video-assisted technique was achieved in all patients. The only complication which developed in one patient was hoarseness for 2 weeks after operation. The hospital stay ranged from 7 to 12 days and there were no serious complications or deaths. These results indicate that video-assisted thoracoscopic surgical interruption is a safe and effective technique for achieving closure of a PDA.

Hepatic surgery

Multiple tumours within the liver are a characteristic feature of hepatocellular carcinoma (HCC)[11]. This study investigated alterations in the histological type and DNA content of multiple nodules of HCC. Both a pathological examination and flow cytometric DNA analysis were performed on 49 resected specimens of multinodular HCC. Some 35 specimens had multiple metastatic satellite nodules around the main tumour (group 1), while 14 had two solitary nodules in different segments without satellite nodules (group 2). In group 1, 28 of 35 showed a single DNA index while seven revealed two different DNA index in the main tumour. The histological type, cytological grade and DNA index were equivalent between the main and satellite tumours in 35, 31 and 34 of 35 samples respectively. In group 2, all tumours showed a single histological type, cytological grade and DNA index in each nodule. The histological type was identical in 12 of the 14 pairs of nodules, but the cytological grade and DNA index were different in six and 12 respectively. The patients in group 2 showed a significantly higher 5-year survival rate than those in group 1 (65 *versus* 27 per cent, $P<0{\cdot}05$). This study indicates that the cytological grade and DNA content are useful in distinguishing multicentric occurrence from intrahepatic metastasis in HCC.

The concept of injury in liver regeneration after partial hepatectomy, and why hepatocytes that have not been directly injured regenerate, remain unclear[12]. It is known that shear stress resulting from blood flow plays an important role in the mechanism of remodelling blood vessels, and portal pressure reflects shear stress. This study was conducted to determine whether acute portal hypertension (APH) can become a trigger of liver regeneration as shear stress following partial hepatectomy in a rat model. Portal pressure became raised immediately after 70 per cent and 90 per cent hepatectomy, peaking on postoperative day 3, and thereafter decreasing in proportion to the diminution of liver regeneration. The portal pressures after 90 per cent hepatectomy were significantly higher than those after 70 per cent hepatectomy even on day 7 after operation, while those of the portacaval shunt groups decreased following shunting both with and without 70 per cent hepatectomy. The liver:body weight ratio also decreased in the portacaval shunt both with and even without 70 per cent hepatectomy. The gradient expressions of class I antigen on sinusoidal endothelial cells (SEC) were found only in the periportal area, which has the highest portal pressure in healthy rat liver. However, after hepatectomy these expressions were detected from the periportal area to the central venous area. These results suggest that APH as shear stress following partial hepatectomy may become a trigger not only of hepatocyte regeneration but also of SEC regeneration, and that surplus APH induces liver dysfunction.

Pancreatic cancer

To clarify the histological status of the pancreas tail after pancreatoduodenectomy, fibrosis, islets of Langerhans, and A, B and D cells were examined histometrically in surgical cases of pancreatic cancer[13]. The same investigations were also performed during an autopsy examination of the pancreas tail of survivors of surgery who had had either pancreatoduodenectomy or total pancreatectomy with segmental autotransplantation (SAT). In the surgical cases, fibrosis and the islet percentage were significantly higher while the B-cell ratio was significantly lower compared with those in cases of non-pancreatic cancer. In addition, in patients with pancreatic cancer, the fibrosis and islet ratio in the group with a blocked pancreatic duct were higher while the B-cell ratio was lower than in the group with an open pancreatic duct. A direct relationship between the islet ratio and the degree of fibrosis, and an inverse relationship between the B-cell ratio and the degree of fibrosis, were thus found. From the autopsy cases, the fibrosis progressed and the islet ratio increased following pancreatoduodenectomy, but after SAT only the islet ratio increased at autopsy compared with the time of surgery. The progression of fibrosis after pancreatoduodenectomy thus suggests the presence of some problems in both the surgical method and postoperative management.

Destruction of the basement membrane is mandatory for tumour spread, and matrix metalloproteinases (MMPs) are known to be implicated in colon cancer invasion and metastasis by digesting type IV collagen, a main component of the basement membrane[14]. The current study analysed the expression of MMP-2 and MMP-9 in pancreatic cancer tissues. Frozen specimens of pancreatic cancer ($n=10$), a liver metastatic nodule from pancreatic cancer ($n=1$) and normal pancreas ($n=3$) were homogenized and analysed by zymography. The activated form of MMP-9 (82 kDa) was detected in all of the normal and malignant tissues, while the activated form of MMP-2 (62 kDa) was detected in all of the samples of pancreatic cancer and its metastatic tissue but not in normal pancreatic tissue. These results indicate that expression of the activated form of MMP-2 may be specific to pancreatic cancer, while that of MMP-9 may be unrelated to it.

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Annales de Chirurgie

Digest

For this quarter's digest, Dr Denis Castaing, Editor of *Annales de Chirurgie*, chooses the best from issues 2, 3 and 4 of 1997. A reciprocal digest written by our European Editor, Mr Colin Johnson, appears in the French journal.

Oesophagus and stomach

To determine the prognostic significance of the histopathological response to preoperative radiochemotherapy in patients with locally advanced oesophageal cancer, an open prospective study was reported by Thomas *et al.*[1], from Marseille. Between 1989 and 1995 243 patients were treated; 134 were operated on immediately, 52 had an operative contraindication and 57 had two courses of radiochemotherapy. Radiochemotherapy included two cycles of continuous 5-fluorouracil from days 1 to 5 and from days 22 to 26, cisplatin on day 1 and day 22, and 15 Gy from day 1 to day 5 and from days 22 to 26. There were nine non-responders who were not operated on. Some 48 patients (eight women; mean(s.d.) age 56·6(8·4) years) underwent oesophagectomy after induction therapy for oesophageal squamous cell carcinoma ($n = 38$) or adenocarcinoma ($n = 10$). The disease-free survival of these patients was correlated with the histopathological findings. Histopathological response was assessed on the operative specimens by routine examination of serial thin sections, each 5 mm, along the total oesophageal length, the resection margins and the lymph node dissection. A wide interindividual variability was observed in the effects of radiochemotherapy: variable grading regression and the possibility of dissociated effects on the various targets, i.e. tumour size, adenopathy and vessel invasion. The 5-year disease-free survival rate was 22 per cent (median 20 months) for the 48 patients who had resection. The presence of a complete histopathological response ($n = 12$) did not preclude metastatic spread in half the cases. Furthermore, it did not result in improved survival when compared with that of non-responders. Survival of patients who had a complete or major oesophageal response ($n = 29$; 35 per cent at 5 years) was significantly lower than that of patients who were operated on during the same period for a superficial oesophageal cancer at presentation ($n = 29$; 57 per cent at 5 years; $P = 0·03$). By multivariate analysis according to the Cox model, downstaging of the primary tumour was not identified as an independent predictor of disease-free survival. The authors' conclusion was that pathological assessment of tumour regression on the operative specimen provides little prognostic information.

Moreaux *et al.*[2], from Paris, reported a series of six patients operated on for a carcinoid tumour of the stomach. Synaptophysin was the most sensitive marker and secretion of serotonin was detected in two patients. To review the clinicopathological characteristics, prognostic factors and optimal management, the patients were separated into two groups according to the histological type of the tumour: first, sporadic tumours, including carcinoids ($n = 2$) and neuroendocrine carcinomas ($n = 2$); and second, gastrin-promoted tumours ($n = 2$). In the first group, patients with a small and well differentiated tumour revealed by gastrointestinal bleeding were treated by wedge excision and are alive without recurrence at 24 and 22 years; the patients with large, invasive and poorly differentiated tumours were treated by subtotal ($n = 1$) and total ($n = 1$) gastrectomy and died 1 and 3 years after with metastases. In the second group, one patient with a small asymptomatic carcinoid tumour revealing chronic atrophic gastritis was treated by endoscopic resection, without recurrence at 3 years; another patient with asymptomatic multifocal carcinoid tumours associated with Zollinger–Ellison syndrome and multiple endocrine neoplasia type 1 was treated by total gastrectomy and is alive without recurrence 7 years later. No patient had carcinoid syndrome. The authors concluded that sporadic carcinoids producing serotonin and neuroendocrine carcinomas are life-threatening tumours and need aggressive surgical therapy. Their prognosis depends on tumour size, histological differentiation and mostly on tumour extension. In contrast, gastrin-promoted carcinoids do not result in disseminated disease and death. In this group, a conservative approach seems appropriate.

Intestinal surgery

Functional results of total colectomy and ileorectal anastomosis for colonic inertia are often impaired by postoperative obstruction and diarrhoea. To avoid these postoperative complications, Costalat *et al.*[3], from Montpellier, propose a subtotal colectomy with caecorectal anastomosis (Deloyers procedure) preserving the ileocaecal junction. This series, from 1989, included 18 consecutive patients (17 women; mean age 54 (range 35–75) years) with intractable constipation. Mean preoperative bowel frequency was two movements every month. Colonic inertia was defined as diffuse marker delay during transit study without obstructed defaecation on manometry or digitalized rectography. Six patients underwent total colectomy and 12 had a subtotal colectomy. Rectocele ($n = 10$), and rectal ($n = 5$) and uterus ($n = 6$) prolapse were treated at the same operation. The postoperative course was uneventful after subtotal colectomy but bowel obstruction requiring laparotomy (two division of adhesions and one bowel resection) occurred in three patients after total colectomy. Mean(s.d.) postoperative daily stool frequency after total colectomy (4·2(1·2)) was higher than that after subtotal colectomy (1·2(0·1). After total colectomy half the patients needed antidiarrhoeal treatment and diet, two had rectal evacuation difficulties despite liquid stools, one had episodic incontinence and four had persistent abdominal pain. Compared with total colectomy, the functional results of subtotal colectomy were significantly better: regular normal transit without diet or treatment in nine patients, three had rectal emptying difficulties that were easily treated by mild laxative therapy and only two had persistent abdominal pain.

Grandjean *et al.*[4], from Lyon, report a prospective study on 26 patients with complex anal fistula operated on between July 1993 and March 1995 to evaluate the use of magnetic resonance imaging (MRI) for treatment and follow-up. The patients selected had a high trans-sphincteric or suprasphincteric fistula with one or more previous definitive attempts at treatment ($n = 15$) and/or severe anal or rectal fibrosis ($n = 11$). The anal suppuration was chronic in 21 patients and acute in five with abscess. Patients with Crohn's disease were not included. For 14 of these patients who had long-term seton drainage, postoperative MRI was used to assess the quality of the surgical drainage and the course of residual abscess. The overall accuracy of MRI for visualization of the internal opening, and of the primary and secondary tracts was 84 per cent, when compared with surgical data. The sensitivity and specificity were 100 per cent for the detection of horseshoe fistulas ($n = 8$). For the 14 patients followed by MRI, only one false positive (presence of sign, absence of symptom) was noted and in five cases the results of MRI modified the previous staged procedure (prolonged seton drainage or new surgical excision). For the 20 patients treated for more than 6 months, the mean follow-up was 18 (median 14) months. Only one recurrence was noted with no loss of follow-up. This study confirms the high degree of accuracy of MRI for mapping high complex fistula *in ano*. MRI is helpful for the monitoring of healing in patients treated with seton drainage and two- or three-stage fistulotomy to preserve continence.

Morbid obesity

Five papers in number 2 of *Annales de Chirurgie* were dedicated to the implications of morbid obesity.

The first paper, by Belachew *et al.*[5] from Huy, Belgium, reports the experience of laparoscopic treatment. Before the first human operation a new prototype of the silicone band for laparoscopic use was devised and a new surgical protocol developed in preliminary animal experiments. Then, from September 1993 to January 1997, 320 laparoscopic procedures for the treatment of morbid obesity with an adjustable silicone gastric band were performed. All the patients were morbidly obese (mean weight 118 (range 92–200) kg). The conversion rate to laparotomy was very low (1·2 per cent). Early complications were 41 cases of alimentary intolerance, one gastric perforation and one subphrenic abscess. Pouch dilatation ($n = 16$) and/or stomach slippage ($n = 23$) have been the only significant late complications. The rate of these complications has been considerably improved by reducing the pouch volume and by using more gastrogastric sutures. Some 80 per cent of patients lost 60 per cent of their excess weight during the first postoperative year. The mean body mass index before operation was 43 kg/m^2, falling to 32 kg/m^2. The authors' conclusion was that postoperative weight loss is comparable in their series of vertical banded gastroplasty and adjustable silicone gastric banding.

The second paper by Fricker[6], from Paris, was on the nutritionist's point of view of the surgical treatment of morbid obesity. Because of the consequences of pathological obesity on morbidity and mortality rates, the weight problems of such patients need to be treated energetically. It is legitimate to consider surgical treatment following repeated failure of medical management. Because of its potential consequences on the patient's nutritional status and lifestyle, obesity surgery should be performed only with strict selection criteria and by using the least aggressive technique, i.e. gastroplasty. The new technique, gastric banding, appears to be more promising in this context. Because of the risk of weight regain after the operation, surgery must be integrated into a more global approach, essentially based on nutrition, psychotherapy and physical activity.

The psychiatric approach to the surgical treatment of pathological obesity was developed in the third paper[7]. Patients are referred for a psychiatrist's or psychologist's opinion in order to detect psychiatric contraindications and to select patients who are able to comply with a weight reduction programme with the help of the operation and who are able to obtain a lasting improvement in their quality of life. The author starts by describing the explicit demand formulated by candidates for gastroplasty, characterized by a high degree of information and motivation. In view of the uncertainties concerning the right advice to be given to this population, an open prospective study was conducted among 109 candidates for gastroplasty. Evaluation of somatic and psychological parameters was performed before the operation and at 6 months, 1, 2 and 5 years. The preliminary results are based on 98 operated patients. The mean(s.d.) body mass index decreased from an initial value of 42·1(0·7) to 29·9(6·7) kg/m^2 at 1 year. The frequency of vomiting decreased with successive evaluations, but nevertheless constituted the major disadvantage of the operation. Evaluation of depression scores, using the Montgomery and Asberg Depression Rating Scale, did not reveal any depressogenic effect of gastroplasty. The other assessment instruments (visual analogue scales and Subjective Quality of Life Profile) indicated a favourable change in numerous dimensions of quality of life. Although it is too early to define any predictive criteria, the author proposes a list of empirical criteria in line with those reported in the literature and defines the role of psychiatrists before and after the operation.

The anaesthetic management of candidates for weight-reducing surgery was developed in the fourth paper by Munsch and Sagnard[8] from Lyon. This management requires a good evaluation of the repercussions of morbid obesity on cardiovascular and respiratory function. The operative risk is increased in obese subjects owing to technical difficulties, mainly during intubation, and to postoperative respiratory and thromboembolic complications. The combination of general and thoracic epidural anaesthesia, when it is possible, is an ideal technique for the anaesthetic management of these patients. It must be performed by specialized personnel in a specialized environment. The objective of this management is to assess the operative risk, and to reduce it to an acceptable level by appropriate preoperative management, taking into account the expected benefit of the surgical procedure.

Masson *et al.*[9], from Lyon, report their experience in reconstruction of the silhouette in patients experiencing rapid and marked weight loss, usually greater than 50 kg, after calibrated vertical gastroplasty. They present a one-stage strategy for reconstruction of the silhouette, combining repair of the abdomen, waist and thighs. This surgical procedure requires precise preoperative assessment and, most importantly, detailed briefing of the patient concerning the operation and expected results. They concluded that intensive preoperative, intraoperative and postoperative psychological support is essential.

Laparoscopic surgery

Sezeur *et al.*[10] conducted a prospective randomized study to compare the risk of bacteraemia in open and laparoscopic appendicectomy. Thirty-five patients with a presumptive diagnosis of acute appendicitis were randomized to conventional open or laparoscopic surgical procedures. Patients who underwent conversion from laparoscopic to open appendicectomy (three patients), those who were human immunodeficiency virus positive, and those allergic to amoxicilline or who had contraindications to laparoscopic surgery were excluded from the study. A total of 32 patients were randomized: 17 to open (group 1) and 15 to laparoscopic (group 2) surgery. There were no significant differences with regard to age, American Society of Anesthesiologists score, symptoms or macroscopic appearance of the appendix. Two patients had a normal appendix, 12 had acute appendicitis, 14 gangrenous appendicitis and four ruptured appendicitis or abscess. All patients received preoperative antibiotic prophylaxis (Augmentin) after which blood cultures (H1) were prepared. Five other blood cultures were performed in standard medium and medium neutralizing Augmentin: at the time of opening the peritoneum (H2), after appendicectomy (H3), after closure of the abdomen (H4), and at 6 h (H5) and 12 h (H6) after operation. Bacterial cultures from the appendix site were performed before (P1) and after (P2) appendicectomy. The operative mortality rate after conventional or laparoscopic appendicectomy was zero. The incidence of postoperative morbidity was four patients in group 1 and two in group 2. No positive bacterial culture was obtained in 17 patients. The distribution of these patients was similar in groups 1 and 2. Samples P1 and P2 were positive in five patients. Nine of 27 patients with a negative P1 culture had a positive P2 culture. There was no significant difference between the two groups with regard to the appearance of the appendix. Only two patients had positive blood cultures at H1. One of them had blood cultures at H3 and H4 positive for a second organism. The authors' conclusion was that a low risk of bacteraemia exists for both open and laparoscopic appendicectomy. This risk did not appear to increase with laparoscopy. Conventional and laparoscopic surgical procedures led to positive peritoneal bacterial cultures after appendicectomy in nine of 27 cases.

The aim of a prospective study, conducted by Court-Payen *et al.*[11] from Copenhagen, Denmark, was to study the impact of biopsies of liver metastases guided by laparoscopic ultrasonography and to evaluate various biopsy techniques. This study was performed on 18 consecutive patients with liver metastases considered to be surgically curable. Any liver lesion discovered by laparoscopic ultrasonography, which could lead to a therapeutic modification, was biopsied with a forceps or guided by ultrasonography using four different techniques. Of 17 patients examined successfully, biopsy was indicated in 12, extension of the surgical procedure was decided in four and laparotomy was avoided in six. The preoperative staging was correct in 15 and incorrect in two cases. Positioning of the puncture needle in the axis of the scanning plane either freehand or in association with an abdominal transducer was effective, without complications. The authors concluded that any liver lesion discovered by laparoscopic ultrasonography which could lead to modification or withholding of surgery should be biopsied, with ultrasonographic guidance in the case of deep lesions.

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Long-term oral administration of branched chain amino acids after curative resection of hepatocellular carcinoma: a prospective randomized trial

THE SAN-IN GROUP OF LIVER SURGERY

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Background Liver cirrhosis is a state of protein calorie malnutrition which may induce various complications. This study aimed to elucidate if long-term nutritional support with branched chain amino acids (BCAAs) is effective after hepatic resection for hepatocellular carcinoma (HCC).

Methods Between 2 and 3 weeks after operation, 75 patients were randomized to receive oral BCAAs (Aminoleban EN) 100 g per day for 1 year, and another 75 patients were assigned to a control group. Mean follow-up times were 35·8 months and 36·0 months respectively.

Results Flapping tremor was less common, body-weight was greater and performance status was better in the BCAA-treated group throughout the 1-year period. BCAA treatment significantly increased red blood cell and serum albumin level in patients with Child grade B and C disease. Substantially similar effects were observed in those with major hepatic resection. Higher Fischer molar ratios were maintained in the treated group. However, there were no differences in cumulative tumour recurrence and survival rates.

Conclusion Long-term oral nutritional support with BCAAs after resection of HCC is beneficial in improving clinical features and laboratory data without increasing the rate of tumour recurrence, particularly in patients with advanced cirrhosis or after major hepatic resection.

Recent advances in liver surgery have drawn attention to the nutritional state and quality of life in patients undergoing hepatic resection for hepatocellular carcinoma (HCC). Most patients with HCC have underlying cirrhosis of the liver and hepatic resection must be performed under these less than ideal conditions[1]. Liver cirrhosis is defined as a state of 'protein calorie malnutrition' with increased catabolism[2–4]. Since malnutrition increases the number of complications associated with cirrhosis, one may speculate that treatment of malnutrition will improve liver function, decrease the incidence of complications, and therefore improve the prognosis of patients with cirrhosis. The administration of branched chain amino acids (BCAAs) is known to correct such malnutrition in patients with cirrhosis[5,6]. However, the effect of long-term administration of BCAAs in patients with cirrhosis has not been studied so far, particularly in those who have undergone liver resection.

This study aimed to clarify whether or not long-term oral administration of BCAAs is effective in terms of clinical features, laboratory data, cancer recurrence and overall survival in patients undergoing hepatic resection for primary HCC.

Patients and methods

Randomization and eligibility

From November 1988 to March 1991, 150 patients who had undergone possibly curative hepatic resection for primary hepatocellular carcinoma (HCC) were randomized 2 to 3 weeks after operation into two groups: those who received BCAA supplementation ($n = 75$) and a control group ($n = 75$). Control patients ate their usual meals and those in the BCAA group drank 50 g Aminoleban EN (Otsuka Pharmaceutical Company, Tokyo, Japan) twice a day in the morning and in the evening in addition to meals for at least 1 year. Sixty-seven patients (89 per cent) in the BCAA group were eligible and 65 patients (87 per cent) in the control group. The causes of ineligibility in each group were non-curative resection in one and four, inability to participate in the study soon after randomization because of complications or referral to distant hospitals in five and four, and non-compliance in two and two respectively

Content of Aminoleban EN

Aminoleban EN contains high amounts of BCAAs, small amounts of other amino acids, ten types of mineral and 14 types of vitamin. Aminoleban EN 100 g contains 27·0 g protein (13·0 g as peptides, 13·0 g as amino acids and 1·0 g as casein), 62·1 g dextrin and 7·0 g rice oil which produce 420 kcal (1758 kJ). Its Fischer ratio is approximately 38

Follow-up

After discharge from hospital, the patients were followed up monthly for 1 year and every few months thereafter. Compliance with Aminoleban administration was carefully monitored. Clinical features and biochemical parameters including plasma amino acid levels were measured at monthly intervals. Neurological status was determined according to Sherlock's criteria[7]. Performance status was evaluated with the Karnovsky scale[8] Tumour recurrence was studied by ultrasonography and computed tomography at 3-month intervals. When tumour recurrence was confirmed, the treatment was left to the judgement of each clinician participating in the study. The mean(s.d.) follow-up times were 35·8(17·9) months in the BCAA

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group and 36·0(17·7) months in the control group (*P* not significant)

Statistical analysis

Data were analysed by either the χ^2 test, Mann–Whitney *U* test or unpaired Students' *t* test. The changes in clinical features such as hepatic encephalopathy, ascites or performance status were compared by the Kolmogorov–Smirnov test[9]. Cumulative survival and intrahepatic recurrence rates were calculated by the Kaplan–Meier method and differences were analysed by the log rank test. *P* values of less than 0·05 were considered to be statistically significant.

Table 1 Clinical background of patients treated with branched chain amino acids and controls

	BCAA treated ($n = 67$)	Control ($n = 65$)
Age (years)		
<50	5	7
50–70	55	45
>70	7	13
Sex		
Male	54	55
Female	13	10
Associated liver disease		
Cirrhosis	46	53
Chronic hepatitis	21	10
Child grade		
A	53	50
B	13	14
C	1	1
Tumour size (cm)		
<3	27	26
3–6	31	30
>6	9	9
TNM stage		
I	24	22
II	35	36
III	7	6
IV	1	1
Liver resection		
Major*	19	26
Minor	48	39

*Resection of one segment or more. BCCA, branched chain amino acid; TNM, tumour node metastasis

Results

Patient characteristics

The two groups of patients were comparable in terms of age, sex, alcohol abuse, underlying liver disease, Child grade, tumour size and tumour node metastasis (TNM) stage, and extent of liver resection (*Table 1*). Also, there were no significant differences between the groups for conventional laboratory data such as peripheral blood analysis and liver function, and plasma amino acid concentrations at the time of randomization.

Compliance and side-effects of branched chain amino acid treatment

Of 67 patients in the BCAA group, 63 continued to take Aminoleban 100 g/day for at least 1 year but the treatment had to cease because of side-effects in three and tumour recurrence in one. Adverse reactions to the BCAA treatment were found in seven patients (10 per cent): nausea and vomiting in four, diarrhoea in one, abdominal distension in one and hypertension in one. Three of these patients could not continue with the BCAA treatment.

Clinical effect of branched chain amino acid treatment

Serial percentage changes in clinical findings in each group are shown in *Table 2*. The rates of flapping tremor and performance status equal to or less than 70 were higher in the control group throughout the year after randomization. Ascites and oedema were significantly less common in the BCAA group but only within the first 3 months. Body-weight was greater in the treatment group at all time points in the first year (*Fig. 1*).

Effect of branched chain amino acid treatment on red cell and platelet counts

Overall, there was a tendency towards higher red blood cell and platelet counts in the BCAA group (*Table 3*). Stratified analyses confirmed that Aminoleban EN was effective in increasing the red cell count in patients with Child grade B and C disease, and platelet count in those with Child grade A disease (*Fig. 2*).

Table 2 Percentage change in clinical features in patients treated with branched chained amino acids and controls

	Time after randomization (months)							*P**	
	1	2	3	4	6	9	12	3 months	Whole period
Flapping tremor									
BCAA treated	4·8	1·6	0	0	1·7	0	0	0·067	0·047
Control	3·6	3·6	1·9	1·9	0	4·2	2·1		
Encephalopathy									
BCAA treated	3·2	0	0	0	0	0	0	0·992	0·919
Control	1·8	1·9	0	0	0	0	2·1		
Ascites									
BCAA treated	6·6	5·0	5·1	9·1	3·4	1·8	0	<0·0001	0·189
Control	14·0	17·9	15·1	11·8	7·4	6·1	2·0		
Oedema									
BCAA treated	3·3	1·7	1·7	1·8	0	1·8	0	<0·0001	0·516
Control	5·3	3·6	3·8	1·9	0	0	0		
Performance status (≤70)									
BCAA treated	6·5	4·8	6·6	5·3	6·6	9·8	10·3	<0·0001	0·047
Control	10·7	8·9	10·7	7·1	8·5	12·5	15·8		

BCAA, branched chain amino acid. *Kolmogorov–Smirnov test (two-tailed, of time matched data)

Effect of branched chain amino acid treatment on hepatic function

There were no substantial differences in conventional liver tests between the two groups (*Table 3*). However, the serum albumin level in the BCAA group was significantly higher in patients with Child grade B or C disease (*Fig. 2*) or in those with major hepatic resection during the first 6 months. There were no significant differences between the two groups in terms of serum ammonia, blood urea nitrogen and creatinine concentrations.

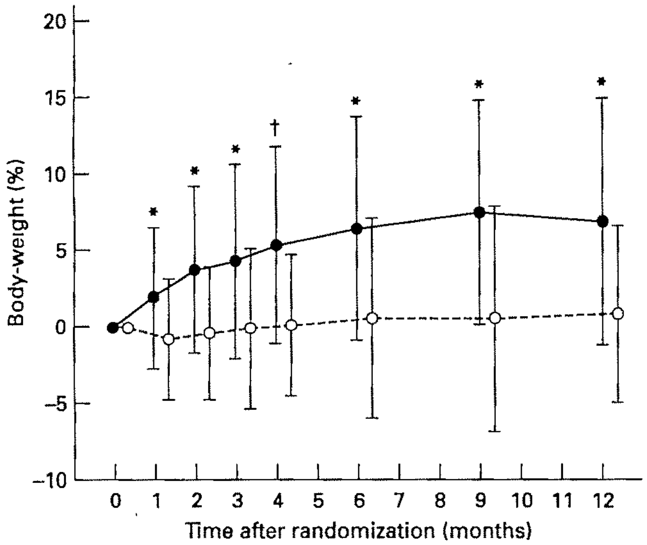

Fig. 1 Percentage changes in body-weight in patients treated with branched chain amino acids (●) and controls (○). Values are mean(s.d.). $^*P < 0.01$, $^\dagger P < 0.001$ *versus* control group (Student's *t* test)

Plasma amino acids and Fischer's ratio

Plasma concentrations of valine, leucine and isoleucine were significantly higher but those of phenylalanine and tyrosine were lower in the patients treated with BCAAs during the first 6 months (*Fig. 3*). Accordingly, the Fischer's molar ratio was significantly higher in the treatment group than in the control group throughout the observation period (*Fig. 4*).

Survival

At the time of final follow-up (September 1994), 34 patients in the BCAA group and 32 patients in the control group had died. The causes of late death in both groups were cancer recurrence in 30 and 23 (*P* not significant), liver failure in three and eight ($P = 0.098$), infection in none and one, and subarachnoid haemorrhage in one and none respectively. The overall cumulative survival rates were no different between the two groups.

Intrahepatic recurrence

Intrahepatic recurrence was found in 39 patients in each group: 58 per cent in the BCAA group *versus* 60 per cent in the control group (*P* not significant). The mean(s.d.) time interval between entry and diagnosis of recurrence was 847(68) days for the former and 814(71) days for the latter group (*P* not significant). There was no significant difference in the cumulative intrahepatic tumour recurrence rates.

Discussion

Malnutrition in liver cirrhosis may be due to reduced nutrient intake, impaired digestion and absorption of

Table 3 Changes in red cell and platelet counts and liver function in patients treated with branched chain amino acids and controls

	Time after randomization (months)							
	0	1	2	3	4	6	9	12
Red cells ($\times 10^4$ per mm^3)								
BCAA treated	369(50)	398(56)	416(61)	431(62)*	422(50)	430(57)	431(59)	432(67)
Control	369(44)	380(52)	403(56)	405(62)	403(61)	413(59)	419(55)	429(51)
Platelets ($\times 10^4$ per mm^3)								
BCAA treated	19·6(11·3)	15 6(7·2)	15·0(6·9)	14·3(6·4)	14·6(6·7)*	14·1(7·1)*	14 6(7·1)*	14·1(6·2)
Control	16·4(7·5)	15·6(5·6)	12 8(4·8)	13·2(4 5)	12·3(3 9)	11·6(3·7)	12·0(3·7)	12 5(3·8)
AST (units/ml)								
BCAA treated	55(36)	67(40)	73(59)	75(78)	66(53)	68(51)	77(67)	87(110)
Control	65(40)	72(47)	95(103)	91(111)	67(51)	71(70)	74(65)	64(44)
ALT (units/ml)								
BCAA treated	47(29)	56(40)	57(47)	67(83)	53(42)	61(49)	67(56)	68(51)
Control	68(56)	60(42)	79(81)	75(76)	63(56)	64(60)	81(84)	66(57)
Bilirubin (mg/dl)								
BCAA treated	0·86(0·54)	0·83(0·86)	0·91(1·05)	0·93(0 65)	0·91(0·79)	0·91(0·42)	0 92(0·44)	0·96(0·53)
Control	1·25(1·58)	0·98(1·72)	1·30(2 66)	1 32(3·05)	0·78(0 46)	0·85(0·57)	0·80(0·33)	0 83(0 39)
Albumin (g/dl)								
BCAA treated	3·54(0·53)	3·77(0·43)*	3·83(0·41)	3·92(0·49)	3·94(0·42)	3·98(0·45)	4·01(0·41)	4·00(0·46)
Control	3·51(0·41)	3·58(0·50)	3·71(0·51)	3·80(0·53)	3·90(0·45)	3 91(0·45)	4 01(0 44)	4·06(0·46)
Cholesterol (mg/dl)								
BCAA treated	127(25)	146(33)	149(29)	155(33)	162(29)	160(27)	162(29)	165(25)
Control	129(33)	141(28)	154(34)	160(30)	155(30)	162(34)	164(25)	167(30)
Ammonia (g/dl)								
BCAA treated	56(28)	48(24)	51(30)	53(31)	64(35)	49(31)	50(23)	51(24)
Control	57(26)	53(26)	49(25)	54(24)	55(31)	53(29)	47(24)	48(26)

Values are mean(s d.). BCAA, branched chain amino acid; AST, aspartate aminotransferase, ALT, alanine aminotransferase. $^*P < 0.05$ *versus* control group (Student's *t* test) nutrients, or impaired metabolism of nutrients in the liver[10,11]. The high incidence of protein deficiency in cirrhosis is to a great extent due to decreased dietary intake and therefore efforts to maintain normal dietary intake are most important in the nutritional care of patients with cirrhosis[10].

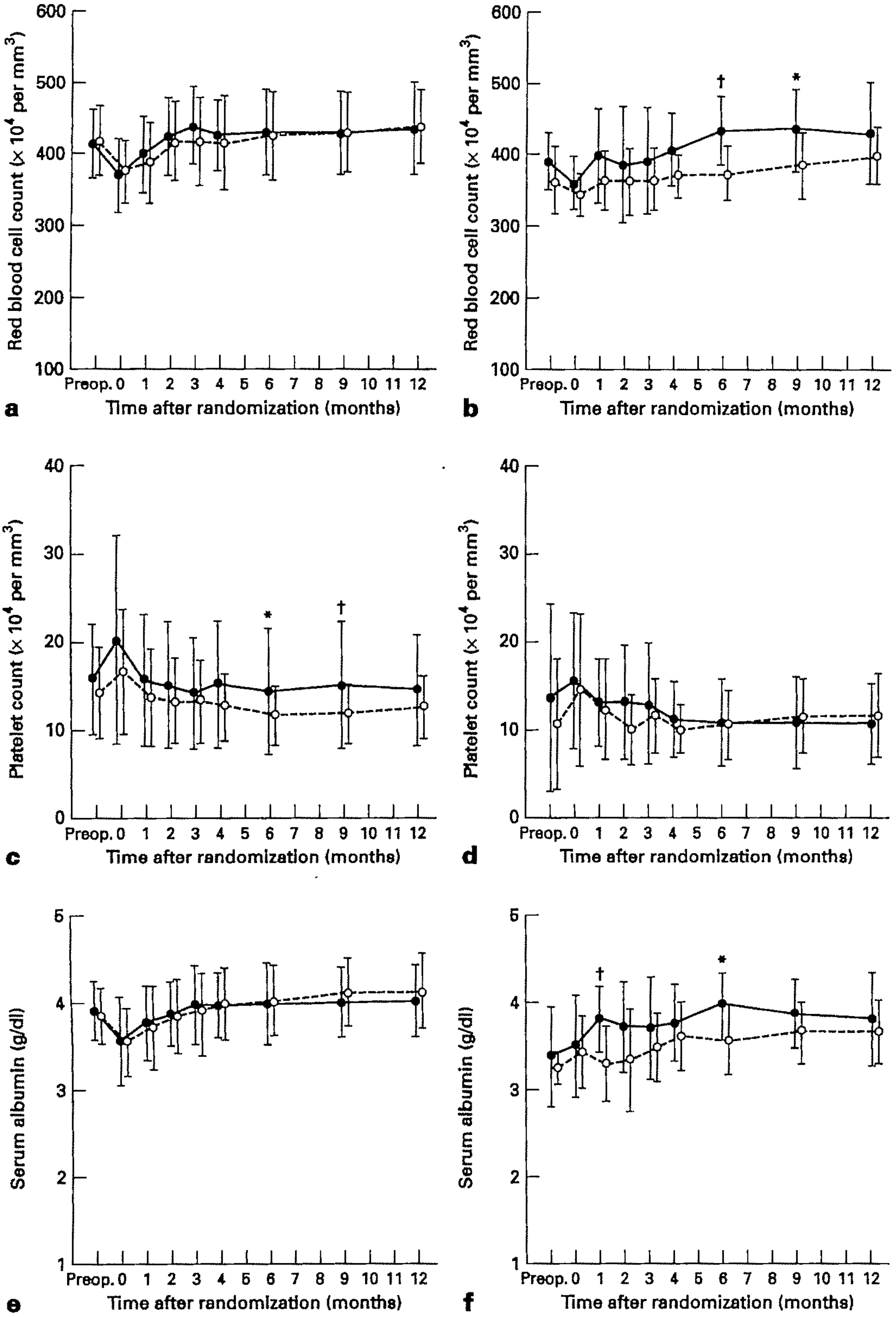

Fig. 2 Changes in red blood cell and platelet counts and serum albumin level in patients treated with branched chain amino acids (●) and controls (○). Severity of disease was Child grade A (a, c and e) or Child grades B and C (b, d and f). Values are mean(s.d.). *$P < 0.05$, †$P < 0.01$ *versus* control group (Student's *t* test)

Experimentally, protein deprivation has profound effects on the liver, including marked depletion of liver protein stores[12], breakdown of hepatocellular protein and RNA, and conversion of polysomes to free ribosomes especially in the rough endoplasmic reticulum where albumin is synthesized[13,14]. Clinically, protein malnutrition is frequently associated with ascites, oedema, impaired function of various organs and vulnerability to infection[15],

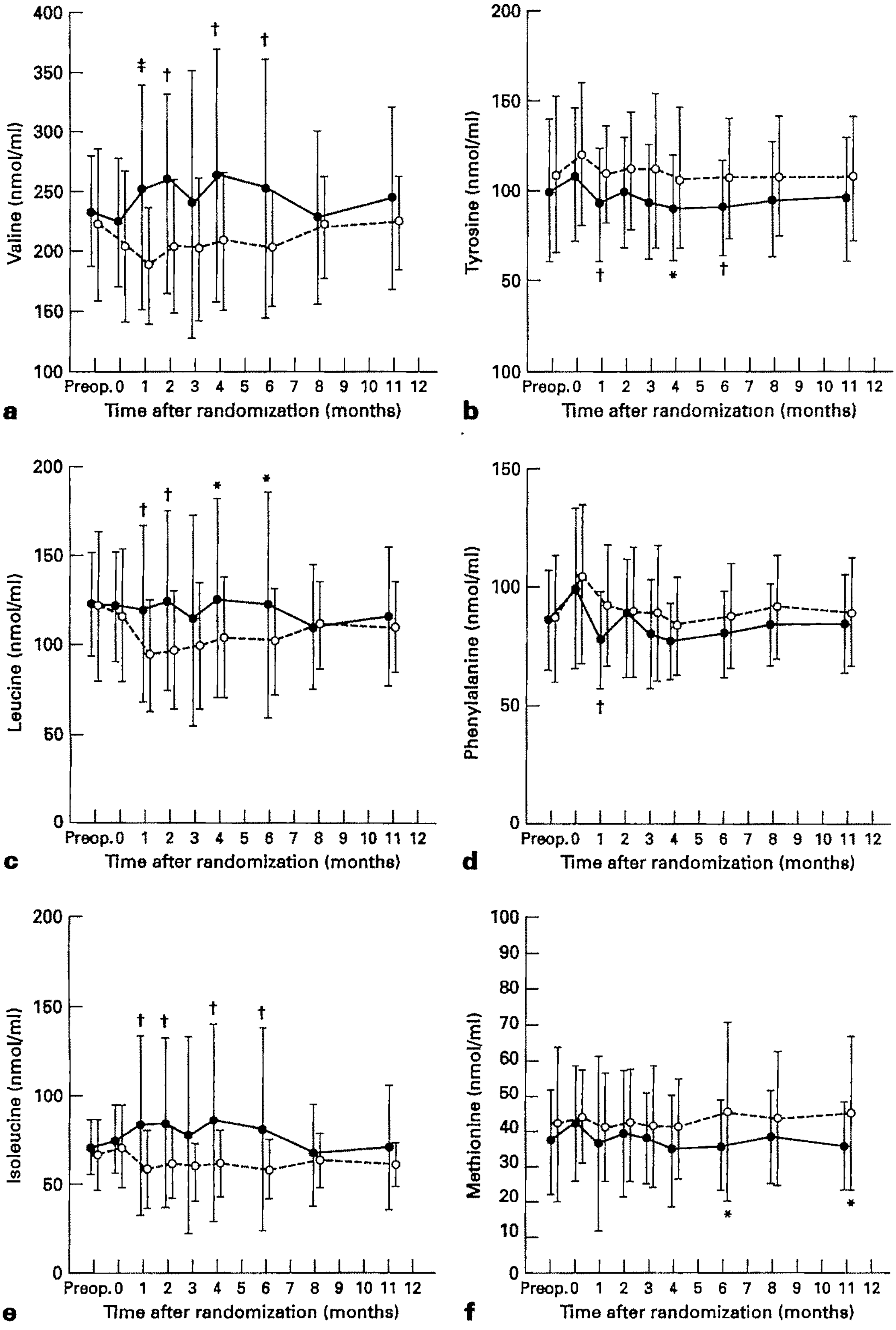

Fig. 3 Changes in plasma amino acid concentrations in patients treated with branched chain amino acids (●) and controls (○). Values are mean(s.d.). $^*P<0{\cdot}05$, $^\dagger P<0{\cdot}01$, $^\ddagger P<0{\cdot}001$ *versus* control group (Student's *t* test)

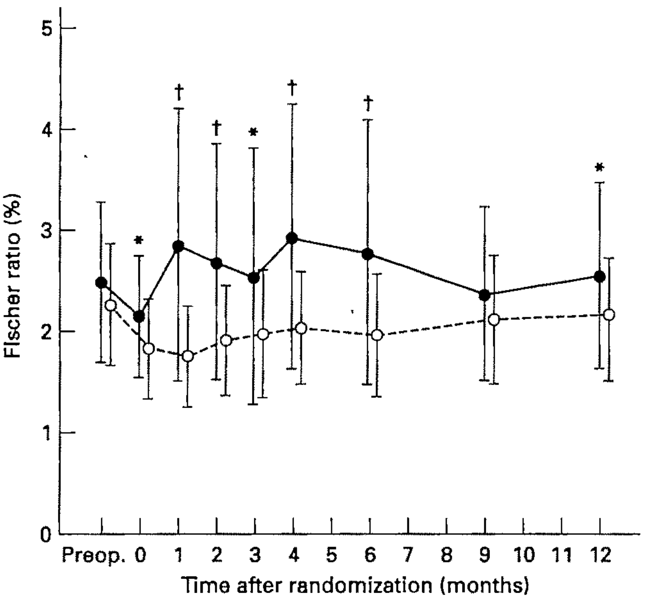

Fig. 4 Changes in Fischer's molar ratio in patients treated with branched chain amino acids (●) and controls (○). Values are mean(s.d.). $^*P<0{\cdot}05$, $^\dagger P<0{\cdot}001$ *versus* control group (Student's *t* test)

or amino acid imbalance which is related to hepatic encephalopathy. In such a context, nutritional support is assumed to be very important in the management of patients with liver cirrhosis.

Based on the false neurotransmitter theory[16,17], Fischer and associates[18] first treated patients with hepatic encephalopathy by supplementation with BCAAs. Since then numerous reports have been published not only confirming the beneficial effect of BCAAs on encephalopathy[19] but finding anticatabolic and protein-sparing or -synthesizing effects in patients with cirrhosis[5,6]. Oral supplementation with BCAAs can be tolerated by patients with severe hepatic dysfunction, and can improve nitrogen balance and psychomotor function[6,20–22]. Although the observation periods in these studies were short, ranging from only 1 to 8 weeks, these results stimulated the present investigation in which BCAA supplementation was performed for 1 year. Fan and associates[23] recently reported a study of nutritional support with BCAAs and other nutrients for 7 days before and 7 days after hepatic resection for HCC. This showed reduced postoperative complications, particularly infectious complications, in the study group. The results of the present study clearly demonstrated beneficial effects of such therapy particularly in patients with severe cirrhosis or in those who had undergone major hepatic resection. These results were in accordance with previous observations that protein synthesis in cirrhotic liver is not necessarily reduced[24,25].

Of obvious concern with nutritional support to patients with malignant disease is the potential for stimulating tumour growth. Most experimental evidence demonstrates that nutritional repletion of malnourished animals and excessive nutrient administration stimulate growth of animal tumours[26]. However, stimulation of tumour growth by exogenous nutritional support has not been documented in humans. Although the present patients were randomized 2–3 weeks after curative resection of HCC, the authors were anxious to determine if supplementation with BCAAs might enhance the growth of potentially residual tumour cells or development of new cancers in the liver remnant[27]. Follow-up of these patients showed that tumour recurrence and overall patient survival rates were not influenced by the BCAA treatment. Schaur *et al.*[28] demonstrated that continuous oral administration of BCAAs to rats bearing Yoshida sarcoma significantly increased survival time by 32 per cent and reduced tumour size by 33 per cent after 3 weeks of growth. Later, Crosby *et al.*[29] obtained a similar result using the same tumour. On the other hand, there are several experimental studies which report that nutritional support by parenteral feeding enhances the growth of rat hepatoma[30,31].

In the light of this study, it is concluded that long-term oral supplementation with BCAAs after curative resection of HCC is beneficial in improving body-weight, performance status and neurological conditions as well as red cell and platelet counts, serum albumin level and amino acid patterns without increasing the rate of tumour recurrence after major hepatic resection.

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Prognostic scoring systems to predict outcome in peritonitis and intra-abdominal sepsis

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Background Early classification of patients presenting with peritonitis and intra-abdominal sepsis by means of objective scoring systems is desirable to select patients for 'aggressive' surgery and to compare results of different treatment regimens. However, none of the existing scoring systems has fulfilled all expectations.

Methods Evaluation of the value of various scoring systems (Acute Physiology And Chronic Health Evaluation (APACHE) II, Simplified Acute Physiology Score, Sepsis Severity Score, Multiple Organ Failure, Mannheim Peritonitis Index (MPI), Ranson and Imrie) was performed in 50 patients. Additionally, scoring systems were combined to obtain a 'combined score' for the prediction of peritonitis-related in-hospital death. Hazard ratios were calculated in a univariate and multivariate analysis.

Results In the univariate analysis all scoring systems, except Ranson and Imrie, predicted the primary outcome. In the multivariate analysis, only the APACHE II score (hazard ratio 6·7) and the MPI (hazard ratio 9·8) contributed independently to the prediction of outcome. All patients with an APACHE II score of 20 or more and a MPI of 27 or more died in hospital.

Conclusion Combination of the APACHE II and the MPI provides the best scoring system fitting clinical goals.

Despite aggressive surgical techniques such as staged relaparotomy and laparostomy, the prognosis of peritonitis and intra-abdominal sepsis is still poor, especially when multiple organ failure develops[1-7]. Therefore, early, objective and reliable classification of the severity of peritonitis and intra-abdominal sepsis is needed not only to predict prognosis and to select patients for these aggressive surgical techniques but also to evaluate and compare the results of different treatment regimens.

In the past two decades, several scoring systems have been developed. In 1981, Knaus and co-workers[8,9] developed the Acute Physiology And Chronic Health Evaluation (APACHE) II score, which integrates 12 physiological variables (clinical findings and laboratory values) with age and chronic health status of the patient. The range of scores varies from 0 to 71, but scores above 40 are uncommon. Because assessment of the APACHE II score is both complex and time consuming, Le Gall *et al.*[10,11] developed the Simplified Acute Physiology Score (SAPS). The SAPS is composed of 14 easily measured physiological variables and the score ranges from 0 to 56. The Sepsis Severity Score (SSS), published by Elebute and Stoner[12] in 1983, consists of four components grading various effects of sepsis. Because both the underlying cause and the secondary effects of sepsis are included, some components are multiply scored, while highly important dysfunction of the pulmonary and cardiovascular organ systems is not assessed. In 1985, Goris *et al.*[13] published the Multiple Organ Failure (MOF) score grading the dysfunction of the pulmonary, cardiovascular, hepatic, renal, nervous, haematological and gastrointestinal systems on a three-point scale. In 1987, Wacha and colleagues[14] published the Mannheim Peritonitis Index (MPI). This incorporates information regarding age, sex, organ failure, cancer, duration of peritonitis, involvement of the colon, extent of spread and character of the peritoneal fluid. The Ranson[15] and Imrie[16] scores, especially developed for grading acute pancreatitis, are assessed within 48 h of onset of the disease and are based on features of shock and tissue injury. Acute pancreatitis is defined as severe when more than three Ranson or Imrie factors are present.

Currently no ideal and generally accepted scoring system exists to determine the prognosis of peritonitis and intra-abdominal sepsis. The present study was performed to evaluate the value of the various scoring systems and to determine how patients at high risk of death are best identified.

Patients and methods

Between January 1994 and February 1995, 50 patients with peritonitis and intra-abdominal sepsis were treated in the surgical intensive care unit (SICU). Twenty-two patients were referred from other hospitals. The mean age of all patients was 58 (range 21–81) years. The male:female ratio was 27:23; there were no important differences between the sexes with regard to age.

Patients were divided into three categories according to the origin of peritonitis: spontaneous perforation ($n = 28$) or postoperative anastomotic disruption ($n = 9$) of the digestive or biliary tract and acute pancreatitis ($n = 13$).

Forty-six patients underwent laparotomy immediately before admission to the SICU or during the first 24 h of intensive care treatment. Initially four patients were treated conservatively, three with acute pancreatitis and one after retroperitoneal perforation during endoscopic retrograde cholangio-pancreatography (ERCP). All patients were critically ill; 44 patients were intubated at admission and needed mechanical ventilation for more than 24 h.

APACHE II, SAPS, SSS and MOF scores were calculated at admission or during the first 24 h of intensive care treatment. In

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Table 1 Definitions of organ failure

Cardiovascular	One or more of the following:	
	Hypotension	≤80 mmHg
		Decrease ≥40 mmHg from initial value
	Use of inotropic support	>4 μg per kg per min dopamine
		>4 μg per kg per min dobutamine
		Adrenaline
		Efedrine
Respiratory	Dependence of ventilation	FiO_2>40 per cent
		PEEP ≥10 cmH_2O
Renal	One or more of the following.	
	Dialysis	
	Urea and creatinine	>25 mmol/l and 450 μmol/l
	Urine output	<150 ml per 8 h

FiO_2, fraction of inspired oxygen, PEEP, positive-end expiratory pressure

these four scoring systems the central nervous system was not graded because of sedation or mechanical ventilation. A fixed value of 15 was determined for the Glasgow Coma Scale or a fixed value of 0 was determined for the central nervous system. Because the authors were mainly interested in assessing local effects of peritonitis when scoring the SSS, only one value for peritonitis or a deep-seated infection was determined (maximum score of local effects was 6); acute pancreatitis was graded as generalized peritonitis. In assessing the SSS, bleeding diathesis was defined if the prothrombin time exceeded the control value by more than 25 per cent. The MPI was scored during laparotomy immediately before admission to the SICU or during the first 24 h of intensive care treatment. The MPI of the patient initially observed for perforation following ERCP was scored using the operative findings at laparotomy performed 3 days later. In scoring the MPI of the three patients with acute pancreatitis who were treated conservatively, exudate was assumed and scored as being 'clear' and infection was scored 'not having diffuse spread'. Additional data regarding age, sex, organ failure and duration of peritonitis were collected at admission. For assessment of renal failure when assessing the SSS and organ failure when scoring the MPI, the definitions used are listed in *Table 1* Because of incomplete data from outside hospitals, Ranson and Imrie scores could not always be assessed within 48 h of onset of the disease; therefore, in all patients with pancreatitis assessment was made after admission to this SICU.

Follow-up was until death or discharge from the surgical ward. The main outcome of the study was peritonitis-related in-hospital death. Scorings according to the various systems were divided at their tertiles or, in case of the Mannheim score, at a previously reported value (less than 27 *versus* 27 or more). Outcome was related to the categories of a scoring system and other baseline characteristics. In the univariate analysis, hazard ratio and 95 per cent confidence interval (c.i.) were calculated by means of the Cox proportional hazard model. Hazard ratios may be interpreted as relative risks In the multivariate analysis variables selected were entered sequentially into the model until no remaining candidate variable had a significance level of 0·10.

Results

Patient group

Twenty-two of the 50 patients died The mean age of non-survivors was 60 (range 37–81) years and that of survivors was 56 (range 21–81) years. Fourteen of the 28 patients treated for a spontaneous perforation died, whereas only two of the nine patients with postoperative leakage did not survive. The patient initially treated conservatively for retroperitoneal perforation following ERCP also died. Six of the 13 patients treated for acute pancreatitis died. All three patients initially treated conservatively for acute pancreatitis survived. Patients' characteristics are listed in *Table 2*.

Table 2 Occurrence of peritonitis-related in-hospital death in relation to patient characteristics and selected scoring systems in univariate analysis

	Death rate		
	Score present	Score absent	Hazard ratio
Male sex	13 of 27	9 of 23	1·3 (0·5–2·9)
Age >60 years	12 of 24	10 of 26	1·5 (0·6–3·5)
Referred	11 of 22	11 of 28	1·1 (0·5–2·5)
Cause*			
Leakage	2 of 9	14 of 28	0·3 (0·1–1·4)
Pancreatitis	6 of 13	14 of 28	0·7 (0·3–1·9)
SAPS ≥16	14 of 16	8 of 34	5·5 (2·3–13)
APACHE II ≥20	15 of 16	7 of 34	7·3 (3·0–18)
MPI ≥27	21 of 35	1 of 15	11·4 (1·5–85)
SSS†			
16–20	9 of 19	1 of 17	6·8 (0·9–54)
≥21	12 of 14	1 of 17	18 (2·3–137)
MOF‡			
6–8	7 of 14	4 of 23	2·6 (0·8–9·0)
≥9	11 of 13	4 of 23	5·7 (1·8–18)
Ranson ≥4	6 of 9	0 of 4	—§
Imrie ≥4	6 of 8	0 of 5	—§

Values in parentheses are 95 per cent confidence interval. *Perforation was taken as reference; †Sepsis Severity Score (SSS) less than 16 was taken as reference, ‡Multi Organ Failure (MOF) score below 6 was taken as reference. §Hazard ratio not calculable. SAPS, Simplified Acute Physiology Score; APACHE, Acute Physiology And Chronic Health Evaluation; MPI, Mannheim Peritonitis Index

Mean follow-up until death or discharge from the surgical ward was 22 (range 3–118) days. The mean length of intensive care stay of non-survivors was 17 (range 3–56) days. The survivors spent a mean of 43 (range 12–118) days in hospital of which 12 (2–48) days were spent in the SICU.

Scoring systems and outcome

Univariate analysis. Table 2 shows the occurrence of peritonitis-related in-hospital death in relation to patient characteristics and selected scoring systems. Male sex and age above 60 years tended to increase the risk of peritonitis-related in-hospital death; also referred patients had a somewhat increased risk. The risk of death due to peritonitis caused by a postoperative leakage or pancreatitis was lower than when peritonitis was caused by a perforation. All higher scores for the various scoring systems except the Ranson and Imrie score were related to an increased risk of death. Particularly, higher APACHE II (hazard ratio 7·3) and MPI (hazard ratio 11·4) scores showed higher hazard ratios for peritonitis-related in-hospital death.

Multivariate analysis. In a multivariate analysis, only the APACHE II (hazard ratio 6·7, 95 per cent c.i. 2·7–17) and the MPI (hazard ratio 9·8, 95 per cent c.i. 1·3–73) scores independently contributed to the prediction of death. When plotted in a Kaplan–Meier curve (*Fig. 1*),

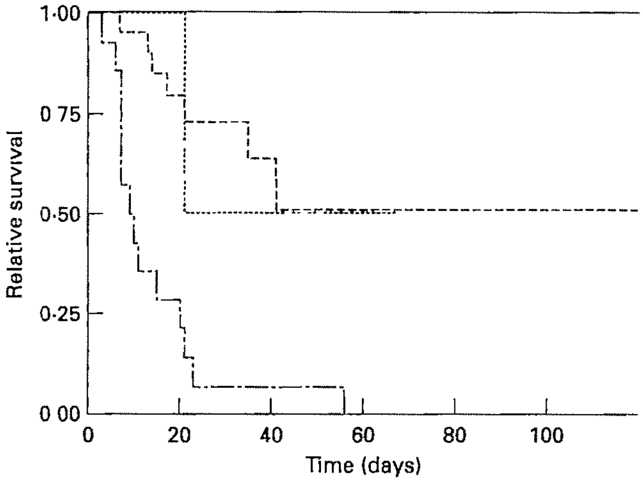

Fig. 1 Survival curves for 50 patients with different Acute Physiology And Chronic Health Evaluation (APACHE) II and Mannheim Peritonitis Index (MPI) scores. ———, APACHE II less than 20 and MPI less than 27; ···, APACHE II 20 or more and MPI less than 27; – – – –, APACHE II less than 20 and MPI 27 or more; –.–.–, APACHE II 20 or more and MPI 27 or more

higher APACHE II scores (16 patients; APACHE II 20 or more) and higher MPI scores (35 patients; MPI 27 or more) contributed independently to the prediction of a higher risk of peritonitis-related in-hospital death. Ultimately, all 14 patients with an APACHE II score of 20 or more and a MPI score of 27 or more died.

Discussion

Despite advances in intensive care medicine and the introduction of aggressive surgical techniques, the prognosis of peritonitis and intra-abdominal sepsis remains poor. In some series mortality rates of more than 60 per cent are reported[1–7]. Early classification of the severity of peritonitis and intra-abdominal sepsis is mandatory to select high-risk patients for aggressive surgery. Probably, in selected cases poor prognosis may even justify decisions not to start or to stop treatment. This study was performed to evaluate the value of existing scoring systems and to combine different scoring systems to produce a 'combined score' fitting clinical goals.

In the univariate analysis, all scoring systems examined, except the Ranson and Imrie score, were relatively accurate for identifying patients at a higher risk of dying from peritonitis. In the multivariate analysis, only the APACHE II score and MPI contributed independently to the prediction of outcome. In the final analysis, combination of the APACHE II score and the MPI independently contributed to a higher risk of peritonitis-related in-hospital death. In several studies concerning patients with intra-abdominal sepsis admitted to an intensive care unit, there was a strong association between increasing APACHE II score and death[17]. Recently Billing *et al.*[18] showed that the accuracy of the MPI was comparable or slightly superior. However, the quality of prediction did not allow individual decision making or limitation of therapy, because 41 per cent of patients with a score over 29 ultimately survived. In this study combination of the APACHE II score and the MPI was far superior to use of the two scores alone. All 14 patients with an APACHE II score of 20 or more and Mannheim score of 27 and above died. Combination of the APACHE II score and the MPI should therefore be the standard classification system for grading the severity of peritonitis and intra-abdominal sepsis.

The choice of discontinuation of treatment of critically ill patients must be made on an individual base. In general, decisions to limit or cease treatment can only be justified in a hopeless situation. Patients with the combination of an APACHE II score of 20 or more and an MPI of 27 or greater seem to be in such a desperate position. If other studies confirm these findings, the APACHE II and MPI scores may become the determining parameters for prediction of outcome in patients with severe peritonitis and intra-abdominal sepsis.

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Randomized controlled trial of prophylactic chest physiotherapy in major abdominal surgery

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Introduction This randomized controlled study evaluated the clinical benefit and physiological effects of prophylactic chest physiotherapy in open major abdominal surgery.

Methods A group of 174 patients received chest physiotherapy including breathing with pursed lips, huffing and coughing, and information about the importance of early mobilization. In addition high-risk patients were given resistance training on inspiration and expiration with a mask. The resistance used during inspiration was $-5\ \mathrm{cmH_2O}$ and that during expiration $+10\ \mathrm{cmH_2O}$. The control group (194 patients) received no information or treatment unless a pulmonary complication occurred.

Results Oxygen saturation on postoperative days 1–3 was significantly greater in the treatment group. Treated patients were mobilized significantly earlier. No difference was noted in peak expiratory flow rate or forced vital capacity. Postoperative pulmonary complications occurred in 6 per cent of patients in the treatment group and in 27 per cent of controls ($P < 0.001$). In high-risk patients the numbers with pulmonary complications were six of 40 and 20 of 39 respectively. Pulmonary complications were particularly common in patients with morbid obesity.

Conclusion Preoperative chest physiotherapy reduced the incidence of postoperative pulmonary complications and improved mobilization and oxygen saturation after major abdominal surgery.

Postoperative pulmonary complications occur in 4·5–80 per cent of patients after upper abdominal surgery, depending on criteria for definition[1–3]. General anaesthesia with controlled ventilation has a negative effect on respiratory function in most patients. Postoperative pain, drugs, immobilization and pre-existing lung disease all play a major role in the development of pulmonary complications. Complications include atelectasis, pneumonia and hypoxaemia[1,4–6].

Chest physiotherapy has been used to prevent postoperative pulmonary complications, particularly in high-risk patients with pulmonary disease, obesity, smoking history, old age, and neuromuscular or musculoskeletal disorders which reduce lung function[1,3,7–13]. However, the clinical benefit of chest physiotherapy is controversial. In 1954 Thorén[3] reported in a controlled trial that the incidence of pulmonary complications after gallbladder surgery decreased with chest physiotherapy whereas Morran *et al.*[14] concluded in 1983 that chest physiotherapy caused more atelectasis but fewer chest infections. No difference in the rate of pulmonary complications was noted in a study that compared two groups of low-risk patients treated before and/or after operation[15]. Few studies are prospective and have an untreated control group[3,14,16–18]. These studies have compared patients after low-risk surgery[3,14,17,18] or have not separated patients at low risk from those at high risk[16].

The aim of this study was to evaluate, in a randomized controlled trial, the clinical and physiological benefit of prophylactic chest physiotherapy before major abdominal surgery with the emphasis on high-risk patients.

Patients and methods

The study included a consecutive series of 368 patients aged 19–92 (mean 53·4) years undergoing elective open abdominal surgery in a gastroenterological unit between February 1992 and May 1993 at Sahlgren's University Hospital, Goteborg. A total of 174 patients was randomized to the treatment group and 194 served as controls. To avoid patient interference a cluster randomization was performed to alternate months Four patients did not complete the study because of reoperation ($n = 1$, control group), non-compliance ($n = 2$, one patient from each group) and death ($n = 1$, treatment group) All patients were given written and verbal information. The study was approved by the Committee of Ethics for human studies at the University of Goteborg

Before operation all patients were classified with an American Society of Anesthesiologists (ASA) score[19] and were also placed in a high- or low-risk group for developing postoperative pulmonary complications[13,20]. Criteria for high risk included age over 50 years and at least one of the following. smoker or ex-smoker for less than 12 months, body mass index (BMI)[21] greater than 30 kg/m², pulmonary disease with need for daily medication, and a history of other medical condition causing reduced ventilatory function.

Treatment group

Patients in the treatment group were seen the day before surgery, given preoperative information and trained by one of four specialized physiotherapists. The protocol consisted of breathing exercises with pursed lips, huffing and coughing hourly, and information about the importance of changing position in bed and early mobilization High-risk patients were given positive respiratory pressure (PEP) masks (Astra Tech, Copenhagen, Denmark) for respiratory resistance training during the breathing cycle. This device comprises a mask with a T valve dividing inspiration and expiration by membranes. Different resistances, according to lung function, were applied to the valves. Pressure during breathing was measured with a manometer $-5\ \mathrm{cmH_2O}$ during inspiration and $+10\ \mathrm{cmH_2O}$ during expiration were preferred. Patients in the treatment group were told to take 30 deep breaths with huffing and coughing between every tenth breath, every hour during the daytime after operation After surgery, physiotherapy continued, adjusted according to the pulmonary status as evaluated by a specialized physiotherapist or the physician in charge. The duration of physiotherapy was 10–15 min before and 15–20 min after operation.

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Control group

Patients in the control group were not given any information or training before operation. After operation, treatment was withheld unless a pulmonary complication was diagnosed. Patients who developed pulmonary complications were given chest physiotherapy with a PEP mask and routine care.

Clinical characteristics of the patients are shown in *Table 1*. There were no significant differences between treatment and control groups with respect to background variables.

Before operation oxygen saturation was measured with an oximeter (Ohmeda 3700; Louisenville, Colorado, USA). Forced vital capacity (FVC) and peak expiratory flow rate (PEFR); were determined in the sitting position with a vitalograph (Wicatest 3; Mijnhardt, Odijk, The Netherlands) and a peak flow meter (Wright, London, UK). The best result of three recordings was used. Assessment of respiratory function was made between 09.00 and 12 00 hours. Chest radiography was performed before operation in patients over 50 years of age or if there was evidence of pulmonary disease. Postoperative chest radiography was performed if there were any symptoms or signs of pneumonia (fever, productive or non-productive coughing, chest pain).

All patients underwent general anaesthesia including endotracheal intubation, and the length of anaesthesia was recorded. Operative procedures are shown in *Table 2*. There were no significant differences between the groups. Patients undergoing surgery for morbid obesity or fundoplication received epidural analgesia for pain relief after operation.

After operation oxygen saturation was measured daily for the first 6 days, except at weekends. Because of unstable respiratory status in some patients, saturation was measured when oxygen treatment was given. In these patients, saturation was recorded as 89 per cent, as an assumed maximum level without oxygen therapy. FVC and PEFR were measured on postoperative days 1, 3 and 6 provided the patient remained in hospital. Use of prophylactic antibiotics, the need for intensive care, rate of mobilization and length of hospital stay were documented. Treatment with bronchodilators and oxygen, and signs of postoperative pulmonary complications, were recorded daily until the patient was discharged. A pulmonary complication was defined as oxygen saturation of less than 92 per cent or two of the following criteria: temperature greater than 38·2°C, pathological lung auscultation, and radiological evidence of pneumonia or atelectasis.

Table 1 Clinical characteristics of patients

	Treatment group ($n = 174$)	Control group ($n = 194$)
Sex ratio (M:F)	72:102	86:108
Mean(s.d.) age (years)	53·5(17·4)	52·9(17·5)
Mean(s.d.) height (cm)	170·9(9·0)	171·1(10·2)
Mean(s.d.) weight (kg)	76·7(22·9)	81·6(28·0)
Overweight*	37 (21)	48 (25)
Smokers*	48 (28)	56 (29)
Lung disease*	18 (10)	23 (12)
Considerable reduction in respiratory function*	7 (4)	4 (2)
High-risk patients*	40 (23)	39 (20)
ASA score		
1	69	67
2	86	91
3	17	28
4	1	2
Missing data	1	6
Mean(s.d.) duration of anaesthesia (h)	3·7(1·5)	3·8(1·8)

*Values in parentheses are percentages. ASA, American Society of Anesthesiologists

Table 2 Surgical procedures in study and control patients

	Treatment group ($n = 174$)	Control group ($n = 194$)
Gastroplasty	31	45
Fundoplication	21	31
Small and large bowel procedures	89	81
Miscellaneous	33	37

Statistical analysis

Data were analysed using a computerized statistical analysis system (SAS; SAS Institute, Cary, North Carolina, USA) and presented as mean(s.d.) or mean(s.e.m.). Differences in the parametric variables between and within the groups were analysed with the Wilcoxon test. For comparison of proportions between the groups, Fisher's exact test was used. The χ^2 test was used for comparison of non-parametric data between the groups. Statistically significant differences were assumed when $P < 0{\cdot}05$.

Results

Postoperative pulmonary complications were diagnosed in ten (6 per cent) of 172 patients in the treatment group and in 52 (27 per cent) of 192 in the control group ($P < 0{\cdot}001$). Pneumonia was diagnosed clinically and radiologically by the physician in charge in one patient in the treatment group and in 13 in the control group ($P < 0{\cdot}05$). Of high-risk patients, six of 40 in the treatment group and 20 of 39 in the control group developed a pulmonary complication ($P < 0{\cdot}001$). The corresponding values in low-risk patients were four (3 per cent) of 132 and 32 (21 per cent) of 153 ($P < 0{\cdot}001$). In the treatment group three of the 36 obese patients (BMI greater than 30 kg/m^2) developed postoperative pulmonary complication compared with 27 of 48 in the control group ($P < 0{\cdot}001$).

Postoperative body temperature, antibiotic therapy and bronchodilators, and the need for oxygen support and intensive care did not differ between the treatment and

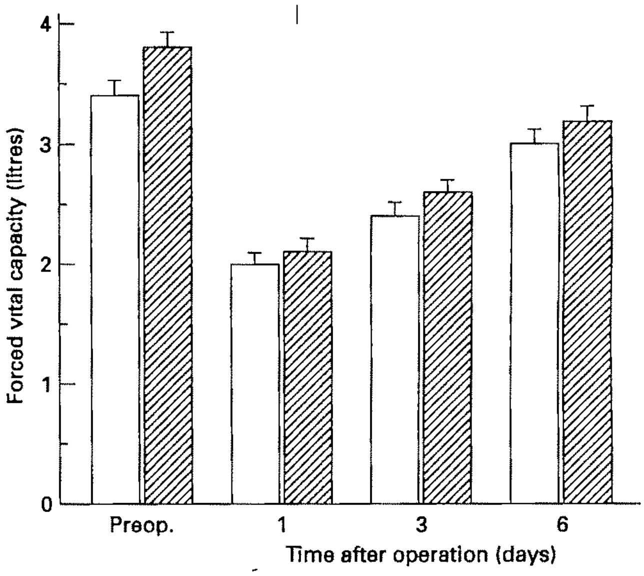

Fig. 1 Forced vital capacity before and after operation. Values are mean(s.d.). □, Treatment group ($n = 72$); ▨, control group ($n = 85$)

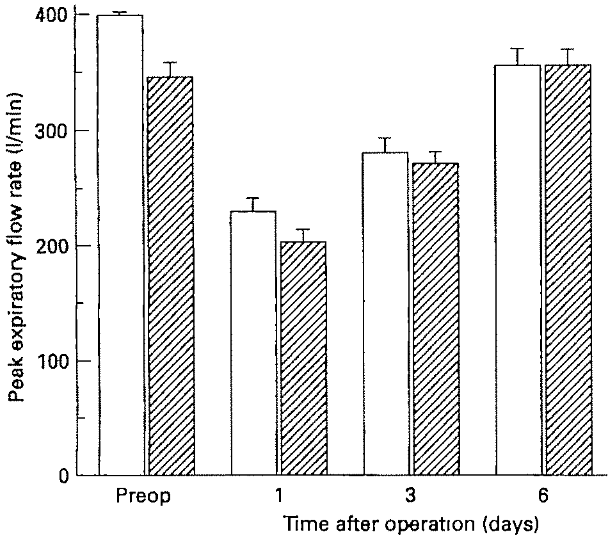

Fig. 2 Peak expiratory flow rate before and after operation Values are mean(s.d.). □, Treatment group ($n = 68$); ▨, control group ($n = 84$)

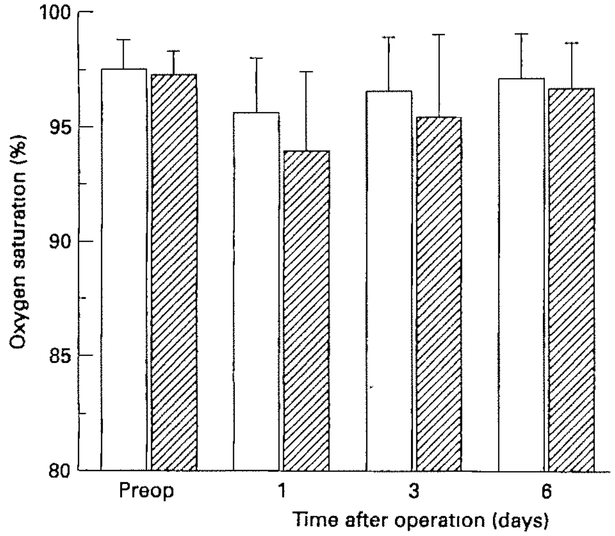

Fig. 3 Oxygen saturation before and after operation. Values are mean(s.e m.). □, Treatment group ($n = 59$); ▨, control group ($n = 80$)

control groups. All patients had a profound reduction of FVC and PEFR after operation, although there was no difference between treated patients and controls. The differences between the groups in oxygen saturation were significant on the first three postoperative days, in favour of the treatment group (day 1, $P < 0.001$; days 2 and 3 $P < 0.05$). Preoperative and postoperative FVC, PEFR and oxygen saturation in patients with complete records are demonstrated in *Figs 1–3*. Oxygen saturation in one patient in the treatment group and in 19 controls was recorded as 89 per cent. Postoperative hospital stay and rate of mobilization are presented in *Table 3*. Patients in the treatment group were fully mobilized earlier.

Discussion

Many studies have demonstrated the effectiveness of chest physiotherapy[3,13–18,20,22–30]. However, only a few have had an untreated control group[3,14,16–18]. The present study indicates that chest physiotherapy given to patients before major abdominal surgery effectively reduces the risk of postoperative pulmonary complications. The rate of pulmonary complications decreased by a factor of 4·5 in all patients and by a factor of 3·4 in high-risk patients. In obese patients, this factor was 7·0, indicating a particularly beneficial effect of physiotherapy. The total incidence of pneumonia was 4 per cent: only one patient in the treated group (1 per cent) and 13 controls (7 per cent). Previous studies have reported rates varying between 1 and 19 per cent depending on the type of patient and surgery[3,9,28].

Table 3 Postoperative hospital stay and rate of mobilization

	Treatment group ($n = 172$)	Control group ($n = 192$)	P*
Duration of hospital stay (days)	8·8(4·5)	9·0(5·1)	n.s
Sitting up in bed (days)	1·1(0·3)	1·1(0·4)	n.s.
Walking in the room (days)	1·4(0·7)	1·8(2·8)	<0·01
Full mobilization (days)	1·8(0·9)	2·4(2·9)	<0·01

Values are mean(s.d.) days after operation. n.s., Not significant *Wilcoxon test

The present study demonstrates that respiratory impairment was less pronounced following preoperative chest physiotherapy. There was no statistical difference in FVC and PEFR between the groups after operation, although the reduction between preoperative and postoperative values was lower in the treatment group. Abdominal surgery decreases the functional residual capacity (FRC), normally by at least 0·5 litres. Together with other negative effects on lung volume, such as pain and immobilization, low FRC predisposes to atelectasis and risk of postoperative pulmonary complications[6,11,13]. The maintenance of postoperative oxygen saturation in the treatment group may therefore be explained partly by the breathing exercises but also by early mobilization.

The measurement of oxygen saturation with oximetry is an easy and safe method for obtaining information on respiratory status, although the results are not fully comparable with those of blood gas analysis and the correlation with risk of postoperative pulmonary complications is poor[4]. Oximetry gives valuable information on optimal oxygen treatment.

The present criteria for defining high-risk patients were not ideal. Obese patients aged under 50 years were by definition at low risk but had a higher incidence of postoperative pulmonary complications than patients with normal weight. This is in contrast to the results of William-Russo *et al.*[12], who concluded that the pulmonary complication rate was not affected by obesity. Other authors, however, have reported a higher rate of complications in overweight patients[1,25,29]. The present observations support the view that obesity is an important risk factor, regardless of age, and that chest physiotherapy is strongly indicated.

Chest physiotherapy has advanced during recent decades. Patients are more active and several new medical devices for breathing exercises have been developed. These devices, like the PEP mask, have led to improved postoperative care after abdominal surgery[20,25]. The choice of treatment selected in this study was based on conclusions from other studies. Hallböök *et al.*[30] concluded that patients having less extensive surgery, such as biliary surgery, had no beneficial effect from chest physiotherapy, as was also found by Bourn and co-workers[15]. However, in the present study a significant reduction of postoperative pulmonary complications was also observed in low-risk patients. Chest physiotherapy, preoperative information, training and postoperative follow-up training are important for low-risk patients undergoing major abdominal surgery. Therefore, preoperative physiotherapy should be instituted regardless of respiratory function. The length of anaesthesia and type of operation are also important determinants of pulmonary complications. Short operations, for example cholecystectomy, do not influence respiration as much as surgery of longer duration.

The high-risk patients in the treatment group in this study used a PEP mask for breathing exercises. Ricksten *et al.*[25] showed that the PEP mask is easier to handle and better than using incentive spirometry and continuous positive airway pressure measurement after upper abdominal surgery. The group using the PEP mask had fewer radiological chest abnormalities. Ingwersen *et al.*[22] published a controlled study on applying resistance to inspiration and expiration. The addition of resistance to inspiration did not appear to improve the outcome after heart surgery.

Patients treated with prophylactic chest physiotherapy demonstrated more efficient respiration, were more active and had a reduced rate of postoperative pulmonary complications. Preoperative chest physiotherapy should be given to all patients before major abdominal surgery but particularly to high-risk patients and those with morbid obesity irrespective of age.

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Short note

Acquired immune deficiency syndrome-related intussusception in adults

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There is a significant incidence of intussusception in patients with human immunodeficiency virus (HIV) infection because of its association with a variety of infective and neoplastic conditions of the bowel[1]. The diagnosis is made increasingly by abdominal computed tomography (CT)[2].

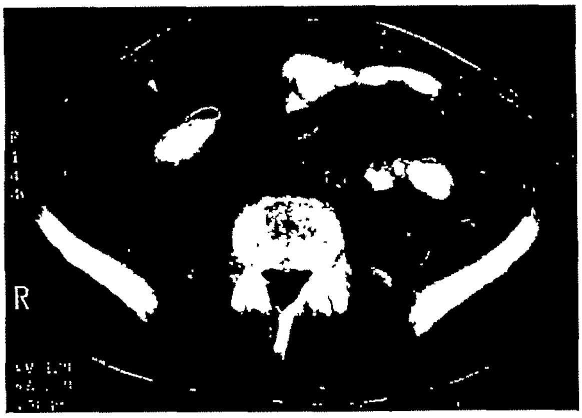

Fig. 1 Contrast-enhanced abdominal computed tomography showing a characteristic 'target mass' (arrow) of an ileocaecal intussusception in the right iliac fossa (patient 1)

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Patients and methods

Four patients with HIV infection and gastrointestinal symptoms of insidious onset were referred for a surgical opinion over an 18-month period. The clinical presentation, diagnosis and pathology are tabulated (*Table 1*). In all patients the leucocyte count was normal and abdominal CT was strongly suggestive of intussusception (*Fig 1*). Three patients with poorly viable intussusceptions underwent emergency right hemicolectomy and one patient had a viable intussusception reduced and subsequently underwent a colonoscopy.

Discussion

There is increasing awareness of the association of intussusception with various acquired immune deficiency syndrome (AIDS)-related conditions of the bowel[1–3]. None the less, the diagnosis is often delayed, largely because of the non-specific and prolonged nature of the symptoms and the extensive differential diagnosis of non-surgical abdominal pathology in these patients. The leucocyte count is rarely raised because of the depressed immune response as indicated by the low CD4-positive cell count in these patients; it is therefore unhelpful in diagnosing bowel inflammation or ischaemia. While intussusception in these patients may follow a subacute course, it could rapidly lead to bowel infarction and peritonitis; hence the importance of early diagnosis.

Plain abdominal radiology rarely demonstrates the cause of bowel obstruction when present. Abdominal ultrasonography is insensitive in the detection of adult intussusception[4]. Barium enema examination is usually not indicated in patients with such non-specific symptoms. Contrast-enhanced CT of the abdomen in addition to displaying features suggestive of an intussusception also provides evidence of extracolonic disease that may assist in the differential diagnosis[2,3,5]. Early abdominal CT is therefore advisable in these patients.

Table 1 Presentation, investigation and pathology of intussusception in four human immunodeficiency virus-positive men

Patient no.	Age (years)	Symptoms	Abdominal signs	CD4 count (cells/mm³)	Diagnostic imaging	Diagnosis	Bowel pathology
1	41	Low-grade abdominal pain and diarrhoea	Localized tenderness and fullness in RIF	60	Abdominal ultrasonography and CT	Ileocaecal intussusception	B-cell lymphoma
2	47	Intermittent lower abdominal pain and diarrhoea	Localized tenderness and guarding in RIF	60	Abdominal radiography, ultrasonography and CT	Ileocaecocolic intussusception	B-cell lymphoma
3	33	Recurrent central abdominal pain with constipation	Localized tenderness and rebound in LIF	120	Abdominal radiography, CT and barium enema	Ileocaecocolic intussusception	B-cell lymphoma
4	33	Crampy central abdominal pain	Bowel obstruction	40	Abdominal radiography, ultrasonography and CT	CMV colitis, colocolic intussusception	Non-specific mucosal inflammation with ulceration

CT, computed tomography; RIF, right iliac fossa; LIF, left iliac fossa; CMV, cytomegalovirus

Intussusception is associated with infectious enteritis, lymphoid hyperplasia, Kaposi's sarcoma and non-Hodgkins lymphoma of the bowel in AIDS. While there is little doubt of the need for bowel resection for a poorly viable or gangrenous intussusception, timely exploration may reveal viable bowel. When a lesion is identified following reduction, resecting the involved bowel should prevent recurrence. In the absence of a palpable lesion, bowel resection is unnecessary and would add to the operative morbidity. When resection is avoided, colonosopic examination in the postsurgical period may reveal a causative mucosal lesion which may be removed endoscopically or resected as an elective open procedure.

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Hand-held Doppler as a screening test in primary varicose veins

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Background Hand-held Doppler is in common use for evaluating varicose veins, but its accuracy in identifying the exact sites of venous reflux is inferior to that of duplex scanning. It has been suggested that duplex should be used to investigate all varicose veins, but this is currently impractical, and should be unnecessary if hand-held Doppler examination were shown to be an adequate screening test.

Methods Eighty-five patients (122 legs) with primary varicose veins were evaluated using a hand-held Doppler in the outpatient clinic, according to a protocol. Patients then had venous duplex imaging.

Results Different methods of assessing the long saphenous vein (LSV) (tourniquet and tapping tests, and examination at and below the groin) had similar sensitivities for detecting reflux (75–86 per cent), and together detected 91 per cent of cases. Six of the nine missed had a competent saphenofemoral junction, and five had low-velocity reflux. Hand-held Doppler assessment missed 11 cases of popliteal fossa reflux; only four involved the short saphenous vein (SSV), and most had low-velocity popliteal vein reflux.

Conclusion Hand-held Doppler examination missed LSV or SSV incompetence in 11 per cent of legs, but these included cases with short-duration and low-velocity reflux of dubious clinical importance.

Planning correct and thorough treatment for varicose veins requires accurate diagnosis of the sites of valvular incompetence[1]. This may easily be done by simple inspection where there is gross long saphenous incompetence, but clinical examination will often miss short saphenous reflux[2], and it is poor for detecting reflux in the deep veins. Hand-held Doppler examination is more accurate than simple clinical assessment[3] and is in common use[1–7], while duplex ultrasonography has become the 'gold standard' for anatomical and haemodynamic assessment of the lower limb veins[8–12].

Some authors have recommended duplex imaging for all patients with varicose veins[13,14], but this is not feasible logistically in most hospitals and should be unnecessary if hand-held Doppler examination could be shown to be an adequate screening test for venous reflux. Selected patients could then be referred for duplex imaging[13]. Studies comparing the accuracy of hand-held Doppler assessment with duplex imaging have already been published[2,14–17]. In general they have sought to emphasize the inaccuracies of hand-held Doppler examination, but a number of points are important in this regard. First, evaluation of hand-held Doppler in a vascular laboratory by research fellows or technicians[16,17] may produce findings which are rather different from those of surgeons and their trainees in a busy outpatient clinic. In addition, different methods of Doppler assessment are used by different surgeons, particularly for the long saphenous system[1,5,6,14,16]. Second, it is the recognition of reflux by hand-held Doppler which matters, rather than identification of its precise origin: duplex imaging can then be requested for precise diagnosis. In the long saphenous vein (LSV), failure of Doppler assessment to differentiate in all cases between saphenofemoral, upper long saphenous, or mid-thigh perforator incompetence[16,17] is unlikely to influence the choice of surgical treatment.

The aim of this study was to evaluate different hand-held Doppler techniques in the outpatient clinic for the detection of long saphenous and popliteal fossa venous reflux, compared with duplex imaging.

Patients and methods

Eighty-five patients referred to the vascular outpatient clinic with primary (previously unoperated) varicose veins were studied. There were 52 women and 33 men, aged 18–89 (median 53) years, with 122 symptomatic legs.

Hand-held Doppler assessment was done according to a pro forma (*Fig. 1*) and findings were recorded immediately by the examiner. Examination was in the following sequence:

1. With the patient standing, the Doppler probe was placed over varicosities in the medial calf, and calf squeezing was done to detect obvious perforator incompetence.
2. The LSV was assessed by:
   (a) Tapping over its course above the knee, with the Doppler probe over a medial varicose vein below the knee ('tapping test').
   (b) A tourniquet (Trendelenburg) test. After elevating the limb a venous tourniquet was applied as high as possible around the thigh, and the patient stood up. With the Doppler probe over a medial calf varicosity, absence of persistent flow signals was taken to indicate either normal veins or control of reflux by the tourniquet. Continuous flow signals were taken to indicate incompetent thigh perforators with LSV reflux (in the absence of calf perforator or short saphenous vein (SSV) incompetence). Flow signals on removal of the tourniquet were taken to indicate saphenofemoral incompetence.
   (c) Examination with the Doppler in the groin skin crease, while squeezing and releasing the calf, to detect saphenofemoral incompetence ('reflux in the groin').
   (d) Similar examination about 10 cm below the groin. The examiner was asked to record whether examination in the groin or 10 cm below was considered easier.
3. The popliteal fossa was examined, first locating signals from the popliteal artery. The probe was then moved while squeezing and releasing the calf to detect signals from the medial and lateral popliteal veins, and the SSV. Features thought to suggest that any reflux heard was in the SSV were

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Preliminary results were submitted to the Association of Surgeons in Glasgow, May 1996
Paper accepted 9 March 1997

(a) Patient name and number. Examiner's name, and date of examination

FOR EACH LOWER LIMB EXAMINED (RIGHT/LEFT SPECIFIED):

(b) **Examination at calf:**
Incompetent direct perforators? Yes No
LSV incompetence on tapping test? Yes No
Saphenofemoral incompetence by tourniquet test? Yes No
(c) **Examination at groin:**
Saphenofemoral incompetence? Yes No
Examination 10 cm below groin:
Saphenofemoral incompetence? Yes No
Which was easier? Groin – 10 cm below – Equal
(d) **Examination behind knee:**
Is there reflux? Yes No
If reflux, do you think this is in Popliteals – SSV – Both
(e) Space for comments

Fig. 1 Pro forma used for hand-held Doppler examination. LSV, long saphenous vein; SSV, short saphenous vein

a clinically obvious SSV and/or disappearance of reflux signals when the Doppler probe was moved proximally.

An audible flow signal lasting 1 s or longer was used as the threshold for diagnosing significant reflux

The hand-held Doppler findings were recorded by a consultant in 103 legs (W.B.C. 77, J.F.T. 26), and by a trainee in 17 (registrar nine, senior house officer eight); the examiner was not recorded in two legs.

At a separate visit to the Vascular Laboratory each patient was imaged using a Diasonics VST Masters (Santa Clara, California, USA) colour duplex scanner with a 5·0-MHz linear array probe. The presence, velocity and duration of any reflux in the LSV (groin, upper thigh, lower thigh), SSV and popliteal veins were determined and these data were stored on a computer database. Extremes of vein size, anatomical anomalies and other points of interest were recorded.

Comparison was made between the diagnoses of reflux using hand-held Doppler assessment and duplex imaging, and between the different methods of hand-held Doppler assessment of the LSV Statistical testing for possible differences in the percentages of 'correct' diagnoses was done using χ^2 analysis.

Results

Table 1 shows the percentage of correct hand-held Doppler assessments for the presence or absence of reflux in the LSV, using different methods of examination. There were no statistically significant differences between these tests in detecting or excluding reflux, although the percentage of false-positive results using the tapping test was noticeably higher than that obtained by any other method. If a positive result from any of the tests was used as the criterion for LSV reflux, this was correctly detected using hand-held Doppler in 89 (91 per cent) of 98 cases. Of the nine cases in which hand-held Doppler failed to detect LSV reflux, six had a competent saphenofemoral junction and five had reflux of relatively low maximum velocity (range 5–11 cm/s) on duplex imaging.

Table 1 Percentage of cases in which hand-held Doppler tests correctly identified the presence or absence of reflux in the long saphenous vein, for the sites specified by duplex imaging

	Percentage correctly identified by Doppler	
	Reflux on duplex	No reflux on duplex
Tourniquet test		
Reflux at groin	81	73
Reflux in thigh	77	84
Reflux in groin or thigh	75	81
Tapping test		
Reflux in thigh	82	63
Doppler in groin		
Reflux in groin	86	82
Doppler 10 cm below groin		
Reflux in groin	81	85

Table 2 Numbers of veins showing reflux on duplex imaging, using different thresholds for the duration of reflux

	Duration of reflux (s)		
	>0·5	>1	>2
LSV in groin	79	78	55
LSV anywhere	100	98	84
Popliteal fossa	56	30	29
Popliteal veins	24	13	5
SSV	31	26	20

LSV, long saphenous vein; SSV, short saphenous vein

In expressing a preference for examination of the upper LSV with the probe in the groin crease, or 10 cm below, examiners recorded a preference for the groin in 15 per cent and for 10 cm below in 17 per cent; 49 per cent had no preference, 9 per cent were undecided and in 10 per cent no response was recorded.

In the popliteal fossa, Doppler assessment correctly detected reflux in only 28 of 39 cases, but correctly excluded reflux in 90 per cent (74 of 82). Predictions about whether reflux was predominantly in the SSV were correct in 18 of 26 cases, and in only five of 13 with popliteal vein reflux. Of the 11 cases of popliteal fossa reflux missed by Doppler, seven involved popliteal vein reflux of short duration (less than 2·1 s), one accompanied by gastrocnemius vein reflux. Of the four cases of SSV reflux missed, three were examined by trainees.

In view of the use of a 1-s threshold for reflux, *Table 2* is presented to show the duration of reflux in all veins found to be incompetent on duplex imaging. Only one of 78 LSVs with groin reflux fell into the range 0·5–1 s, and only two of 100 with reflux anywhere above the knee. The majority of incompetent LSVs demonstrated reflux for greater than 2 s. In the popliteal fossa, use of a 1-s threshold for reflux excluded five of 31 SSVs which would have been judged to be incompetent using a 0·5-s threshold, but many more popliteal veins (11 of 24) exhibited a short duration of reflux.

Discussion

It is reasonable to debate how many of the cases of reflux missed by hand-held Doppler assessment in this study were clinically important. In the popliteal fossa the majority of reflux was due to popliteal veins with relatively short-lived reflux. It is unlikely that their detection would have influenced treatment.

Experienced examiners believe they know when reflux is 'significant' on hand-held Doppler examination, but an attempt at definition is important. Despite the widespread acceptance of a 0·5-s threshold for diagnosing venous reflux, the authors use a threshold of 1 s for several pragmatic reasons. First, there is some evidence[18] that normal veins exhibit reflux for more than 0·5 s. Second, reflux times between 0·5 and 1 s are uncommon in the LSV, as shown in this study, although they are more common in the SSV and popliteal veins. Third, definitive surgery would not usually be considered for a vein which exhibited reflux for 0·5–1 s, because there is almost always much more florid reflux in another system of veins in a symptomatic limb.

The velocity of reflux may also be important, and it is interesting to note that Baker *et al.*[10] did not regard peak reflux velocities of less than 10 cm/s as significant. In practice, low-velocity reflux is often disregarded, and five of the nine cases of LSV reflux missed by hand-held Doppler examination had peak reflux velocities of below 11 cm/s. If these are excluded and one SSV with a peak velocity of 5 cm/s, then only seven incompetent LSVs and SSVs (6 per cent) escaped diagnosis. While low-velocity reflux may be relatively unimportant, there must be a relationship between reflux velocity, duration of reflux, diameter of the vein, and the volume of refluxed blood. The clinical significance of these variables, and the relationships between duration and velocity of reflux and venous hypertension, require further study.

The percentage of cases of LSV reflux correctly diagnosed by hand-held Doppler was similar to that in other studies, which have reported sensitivities of 73–90 per cent[3,15–17], although De Palma *et al.*[14] reported a sensitivity of only 48 per cent for detection of saphenofemoral incompetence. It is important to consider exactly what is meant by 'LSV reflux'. Doppler examination in the groin and 10 cm below will detect only 'groin incompetence', while tapping over the mid and lower parts of the LSV in the thigh tests for reflux lower down. In agreement with Abu-Own *et al.*[19] LSV reflux was observed in patients with no groin reflux, but in whom reflux times and velocities increased distally down the LSV.

On the basis of this study the authors will continue to use hand-held Doppler as a screening test for primary varicose veins, but have abandoned the tourniquet (Trendelenburg) test because it adds little to other tests. Routine use of the 'tapping test' has also been abandoned because of the high number of false-positive results. Occasionally, patients with LSV and SSV incompetence will be missed, mostly those with short-lived or low-velocity reflux. It is important that examiners have adequate experience with hand-held Doppler examination; good teaching and continued supervision of trainees is essential. The authors now refer for duplex imaging all patients with popliteal fossa reflux, those with equivocal Doppler findings (especially if the venous anatomy seems abnormal), and almost all patients with recurrent varicose veins.

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For debate

Lateral rectal ligaments contain important nerves

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The contents of the so-called lateral rectal ligaments are defined differently in surgical and anatomical texts. In surgical texts the middle rectal arteries are referred to as the main structures within them[1-3]. In contrast, the meticulous anatomical work by Sato and Sato[4] has shown that arteries are found in only about 20 per cent of cadaver dissections, whereas nerve branches from the pelvic plexuses, also called the neurovascular bundles, are uniformly constant structures within the ligaments. This view of the lateral ligaments as important nerve-containing structures is supported by clinicophysiological results after sphincter-saving surgery reported in the Japanese literature[5,6].

The autonomic nerve supply of the lower rectum has been postulated to arise from the pelvic side wall plexuses[4,7]. The close relationship of the ligaments to the pelvic plexuses, which contain merging sympathetic and parasympathetic nerve fibres, makes the dissection of the ligaments crucial in maintaining genitourinary function[8,9].

However, Enker *et al.*[10] recently considered the ligaments to be structures that are surgically developed by medial traction during operation. This view has been further established by the same group after cadaveric studies[11].

The objective of this investigation was to study the nervous contents of the lateral rectal ligaments in a surgical series of patients.

Patients and methods

Ten patients, four men and six women, aged 71–86 years, underwent operation for rectal carcinoma by total mesorectal excision in two Swedish hospitals. The lateral rectal ligaments were identified, dissected, photographed and then biopsied for histological analysis. Biopsy specimens were taken from one side in seven of the patients and from both sides in three. The specimens were analysed by routine histology and nerve staining.

Surgical technique

When performing total mesorectal excision for rectal carcinoma the mesorectum is mobilized from the presacral hollow forwards[5]. The lateral pelvic plexuses are encountered anterolaterally on each side.

The often thin structures, usually referred to as the lateral ligaments, seem to arise from the pelvic plexuses and bridge over into the mesorectum. They are often found 2–3 cm below the deepest part of the peritoneal reflection. In the authors' experience they can be identified in almost every patient operated on for rectal excision. To help the surgical perception by trainees of these structures a diagram has been developed (*Fig. 1*).

In all cases the ligaments were cut at two points, close to the pelvic plexus and to the mesorectal fascia, and the small specimen was sent for histological analysis.

Results

The lateral rectal ligaments were identified bilaterally in all patients. The structures could be visualized on photographs (*Fig. 2*). The histological findings were of clear nerve structures, fatty and fibrous tissue in all 13 specimens and of small blood vessels in two (*Fig. 3*).

Discussion

It seems logical that the rectum, with its complicated function and physiology, has a rich autonomic nerve supply. The observations of the lateral ligaments arising from the autonomic lateral pelvic plexuses and their content of nerve fibres support both this view and earlier

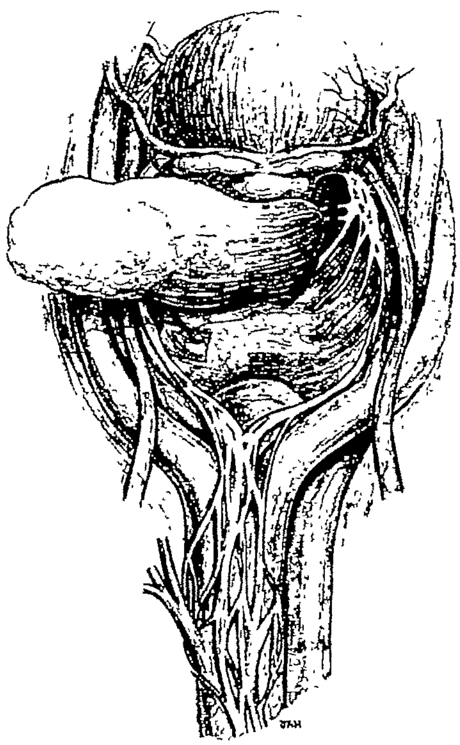

Fig. 1 Diagram of the autonomic nerve supply in the pelvis. Surgeon's view from the head end of the patient. Two nerve fibres in the right lateral rectal ligament are seen divided as they bridge over from the pelvic plexus to the rectum. Reproduced with permission from Springer

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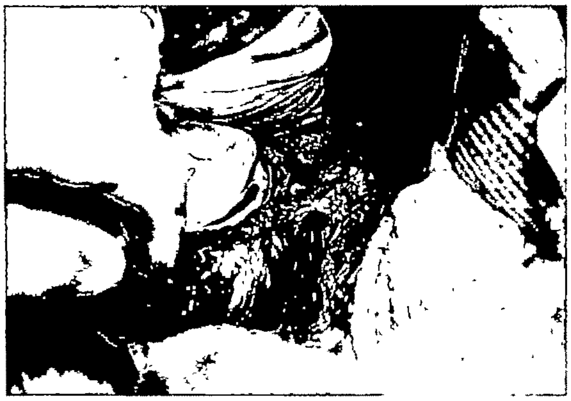

Fig. 2 Photograph of the right lateral rectal ligament (indicated by scissors), seen bridging over from the lateral pelvic side to the mesorectum in a 71-year-old man operated on for rectal carcinoma

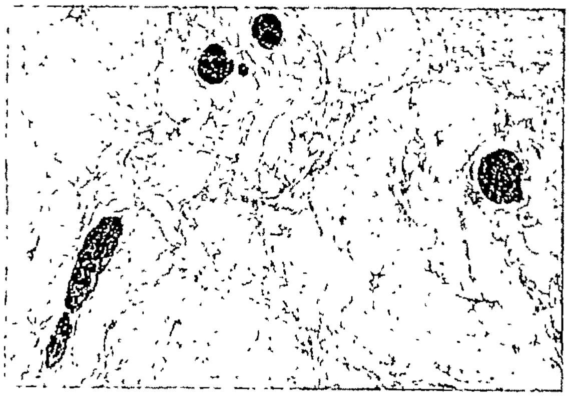

Fig. 3 Light micrograph of soft tissue biopsy from a 73-year-old woman operated on for rectal carcinoma. Immunohistochemical staining for S-100 protein. Multiple nerve fibres (brown colour), surrounded by fat, are visualized

anatomical work. In fact, the lateral ligaments encountered in rectal surgery correspond well to the medical portion of the lateral ligaments of the rectum as described by Sato and Sato[4]. Accordingly, the authors consider the ligaments to be real anatomical findings and not merely surgically developed structures, as recently described[10,11].

These anatomical observations are of surgical technical importance. The dissection around the mesorectum must proceed carefully and the lateral ligaments and pelvic plexuses should be identified in order not to sever the latter. Division of the ligaments bridging over to the rectum must be performed precisely, because 'tenting' of the main neurovascular trunks may lead to inadvertent injury to them. Gross clamps should therefore be avoided. In the area close to the nerves, sharp scissors dissection with gentle diathermy only on identified vessels is recommended.

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Population-based study of the treatment and prognosis of carcinoma of the rectum

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Background Few population-based studies address the issue of treatment of carcinoma of the rectum (15 cm or less from the anal verge) both from surgical and epidemiological aspects.

Methods Some 827 patients were analysed in the cancer registry of the Côte-d'Or (Burgundy, France) from 1976 to 1990 (493 931 inhabitants).

Results Resection for cure increased from 57·2 per cent before 1981 to 77·0 per cent after 1985 ($P < 0.001$), and the proportion of Dukes A and B cases from 35·8 to 52·5 per cent ($P < 0.001$). Among patients resected for cure, continence-preserving resections were performed more frequently during the 1986–1990 period (48·0 per cent) than during the two previous 5-year periods (20·0 per cent; $P < 0.001$), more often in women, in the upper half of the ampulla and for tumours of less than 45 mm. The operative mortality rate after curative surgery decreased from 13·9 to 3·7 per cent ($P < 0.001$) between the first and the last period whereas the 5-year crude survival rate rose from 25·8 to 42·6 per cent ($P < 0.001$). Age, stage of disease and period of diagnosis were independent prognostic factors of death in a relative survival model.

Conclusion This study indicates that significant advances have been achieved at a population level in the treatment of rectal cancer in terms of diagnosis, continence-preserving procedures and survival.

Carcinoma of the rectum is a common condition[1] and its prognosis continues to be poor, especially in international population-based studies[2–4]. Surgery remains the primary treatment and prognosis depends primarily on the extent of the tumour at the time of diagnosis. Over the past 20 years, numerous developments have taken place in diagnosis, surgical options and adjuvant therapy, with increasing emphasis being placed on sphincter preservation and improvement of quality of life[5–7]. Surgical advances have included stapling devices and operative techniques like coloanal anastomosis. Initiated in specialized centres they have progressively spread to general surgical practice but their impact in a total population is not known. Results from specialized centres may be misleading because of referral bias.

Community-based studies, recording all diagnosed cases in a well defined population, may better assess real improvements in the management of rectal cancer. Such studies are rare because they require accurate and detailed data collection which is seldom done systematically in cancer registries. This study was undertaken to determine changes in therapeutic approaches, stage at time of diagnosis and prognosis of rectal carcinoma in a well defined population over a 15-year period.

Materials and methods

Population

The population-based Cancer Registry of the Côte-d'Or area (Burgundy, France) records all digestive cancers diagnosed among residents (493 931 inhabitants; 1990 census). This cancer registry includes accurate data relative to the clinical features, treatment and follow-up of patients. Between January 1976 and December 1990, 827 rectal carcinomas located within 15 cm of the anal verge were recorded. Cancers of the rectosigmoid junction ($n = 535$) and of the anal canal ($n = 83$) were not included in this study. Adenocarcinoma was found in 95·4 per cent of cases ($n = 789$), lymphoma in 11 cases, anaplastic carcinoma in ten, malignant tumour in seven and carcinoid in one The age-standardized incidence (world population) was 9·7 per 100 000 per year for men and 4·6 per 100 000 per year for women.

Data were collected from all public and private pathology laboratories of the area ($n = 3$), from local ($n = 5$) and university ($n = 2$) hospitals, from clinics ($n = 4$), surgeons, gastroenterologists, general practitioners in private practice as well as from public administration (death certificates). No cases were registered through death certificates alone, but these were used to identify missing cases A copy of the pathology report was provided by the three pathology laboratories, which all use the same computerized form, providing standardized and predefined information.

Ninety items were collected for each patient as soon as a diagnosis of cancer was made. Clinical data collection was made either immediately during staff meetings or later with the help of the physicians concerned.

Variables studied

For all patients, clinical variables included sex, age at diagnosis, location of the tumour in the rectum, size, histological type, treatment and stage at diagnosis. In case of operation, stage at diagnosis was considered as equivalent to stage at operation since patients were operated on within the month following diagnosis. The tumour classification was based on the distance between the anal verge and the lowest part of the tumour. When the distance was less than 8 cm, the tumour was classified as low. When the tumour was 8 cm or more from the anal verge, it was classified as high.

Surgical procedures were divided into curative and palliative. Surgery was considered curative when the surgeon deemed the tumour completely removed and the distal margins were free from cancer with no evidence of distant metastasis. Distal margins were measured and recorded by the pathologist before tissue fixation of the unpinned specimen Surgical procedures were divided into continence-preserving resections and those in

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which continence was not preserved. Hartmann's procedure ($n = 11$) was classified into continence preserving or non-preserving depending on the later restoration of continuity. Transanal surgery and endoscopic procedures were not defined as surgical resections but as transanal excisions. Operative deaths were defined as those occurring within 30 days after surgery.

The extent of the disease was based on hospital records and pathological reports. Surgically-removed tumours were categorized according to Dukes classification[8]. Non-operated patients without detectable metastasis were recorded as unclassified and their specific impact on survival was included in the multivariate analysis. In December 1994, the life status of 802 patients (97·0 per cent) was available. Twenty-one patients with incomplete follow-up were censored and four patients with no survival information were not included in the survival analysis.

Statistical analysis

Associations between categorical data were analysed using χ^2 tests for homogeneity and trend tests. Factors associated with a choice of sphincter-preserving or non-sphincter-preserving resection were analysed through a non-conditional logistic regression[9] in the group of patients resected for cure. Transanal excisions and trans-sacral approaches were excluded because the choice of procedure was decided before operation. A non-conditional logistic regression was also used to identify the risk factors independently and significantly associated with post-operative death.

The crude survival rates were calculated using the Kaplan–Meier method[10] and were expressed with standard errors. Survival curves were compared using the log rank test. Relative survival rates were also calculated, these being defined as the ratio of the observed survival rate to the expected survival rate derived from the 1983 Côte-d'Or area mortality table.

A multivariate survival analysis was performed using a relative survival model with proportional hazard applied to the net mortality rate by interval[11]. This model makes it possible to calculate relative risks in comparison to a baseline which is the cumulative net hazard calculated from a priori defined intervals. A partition of five 1-year intervals was used in this study. The multivariate models were fitted using a backward procedure. The significance of covariates was tested by the likelihood ratio test. All tests (two-sided) were performed at the 5 per cent level. The computations were performed using BMDP (Los Angeles, California, USA) and EGRET/SERC (Seattle, Washington, USA) software.

Results

Trends in stage at diagnosis

Overall, 167 carcinomas were Dukes A (20·4 per cent), 192 Dukes B (23·4 per cent) and 172 Dukes C (20·9 per cent); there were 48 non-resected tumours with local or regional spread (5·8 per cent), 103 were metastatic (12·6 per cent) and 138 were unclassifiable (16·8 per cent, i.e. non-operated patients without metastasis). The percentage of patients with Dukes A and B disease increased during the study period from 35·8 per cent (106 of 296) in 1976–1980 to 44·6 per cent (125 of 280) in 1981–1985 and 52·5 per cent (128 of 244) in 1986–1990 (P for trend $< 0·001$).

Trends in treatment

Surgical techniques are listed in *Table 1*. The 546 curative procedures were separated into three groups: transanal approaches (12·1 per cent), continence-preserving resection (26·0 per cent) and resection not preserving continence (61·7 per cent). Overall, continence was preserved in 38·1 per cent of patients treated for cure.

Table 1 Techniques used in the treatment of cancer of the rectum from 1976 to 1990

Treatment ($n = 660$)	Surgical treatment Curative ($n = 546$)	 Palliative ($n = 114$)
Transanal approaches		
Transanal excision	46	3
Endoscopy	20	0
Laser	0	3
Continence-preserving resection		
Anterior resection	134	11
Coloanal anastomosis	5	0
Kraske	2	0
Restored Hartmann	1	0
Resection not preserving continence		
Abdominoperineal resection	327	18
Hartmann	4	6
Others	6	4
Other procedures		
Colostomy	0	65
Laparotomy	0	3
Unknown	1	1

Non-operated patients underwent contact radiotherapy ($n = 19$), external radiotherapy ($n = 51$) or symptomatic treatment only ($n = 97$). No chemotherapy was performed as the main treatment of the rectal tumour.

The percentage of operations for cure increased from 57·2 per cent ($n = 171$) during 1976–1980 to 65·6 per cent ($n = 185$) in 1981–1985 and 77·0 per cent ($n = 190$) during 1986–1990 (P for trend $< 0·001$). This increase was the result of a decrease in the number of palliative operations (18·4 per cent ($n = 55$), 13·8 per cent ($n = 39$) and 8·1 per cent ($n = 20$)) and a decrease in non-surgical procedures (24·4 per cent ($n = 73$), 20·6 per cent ($n = 58$) and 14·6 per cent ($n = 36$)) during the same periods.

Adjuvant radiotherapy was performed during the first 5-year period in 18·1 per cent of cancers treated for cure (31 of 171), in 28·1 per cent in the second period (52 of 185) and in 35·3 per cent in the third (67 of 190) (P for trend $< 0·001$). Radiotherapy was given before operation in 18·0 per cent of patients and after operation in 82·0 per cent.

Factors associated with continence-preserving operation among patients resected for cure

Overall, continence was preserved in 29·6 per cent of patients resected for cure. The location of the tumour was uncertain in nine patients; continence was preserved in 123 patients (62·1 per cent) with carcinomas located in the upper half of the rectal ampulla and in only 11 (4·3 per cent) with carcinomas located in the lower half ($P < 0·001$). Continence-preserving resections were performed more often during 1986–1990 (48·1 per cent) than during the two earlier periods (20·0 and 18·9 per cent in 1976–1980 and 1981–1985 respectively) (P for heterogeneity $< 0·001$). Tumour location, period of diagnosis, sex and tumour size were significant factors associated with the choice of continence-preserving resection during the operation in the multivariate analysis (*Table 2*). The probability of continence-preserving resection among women was 2·4 times greater than that of men. Tumours less than 45 mm in diameter were 2·7 times more likely to be associated with a continence-

Table 2 Factors associated with choice of a sphincter-saving resection for cure

Factor	*n*	Odds ratio	*P*†
Sex			
M	298	1	0·005
F	167	2·38 (1·29–4·40)	
Tumour size (mm)			
≥45	269	1	<0·002
<45	196	2·68 (1·44–4·99)	
Location*			
Lower half	258	1	<0·001
Upper half	198	90·85 (39·46–214·58)	
Period			
1976–1980	149	1	<0·001
1981–1985	156	1·30 (0·64–2·63)	
1986–1990	160	9·79 (4·48–21·40)	

Values in parentheses are 95 per cent confidence intervals. Logistic regression was carried out among patients treated for cure, excluding those who underwent transanal and trans-sacral procedures as well as 12 patients with tumours of unknown size. *Location unknown in nine patients. †*P* for heterogeneity (likelihood ratio test)

Table 3 Factors associated with postoperative death among patients resected for cure

Factor	*n*	Relative risk	*P**	*P*†
Age (years)				
<65	166	1	0·021	<0·01
65–74	159	2·40 (0·90–6·43)		
≥75	152	3·61 (1·37–9·52)		
Period				
1976–1980	158	1	0·003	<0·001
1981–1985	159	0·40 (0·18–0·89)		
1986–1990	160	0·23 (0·09–0·60)		

Values in parentheses are 95 per cent confidence intervals. **P* for heterogeneity (likelihood ratio test); †*P* for trend

Table 4 Factors of prognostic significance in carcinoma of the rectum in a relative survival model

	Relative survival	
Factor	Relative risk	*P**
Age (years)		
<65	1	0·003
65–74	1·24 (0·95–1·62)	
≥75	1·59 (1·22–2·07)	
Sex		
M	1	0·388
F	0·91 (0·73–1·13)	
Period		
1976–1980	1	0·001
1981–1985	0·75 (0·59–0·95)	
1986–1990	0·62 (0·47–0·82)	
Dukes stage		
A	1	<0·001
B	1·87 (1·04–3·37)	
C	5·87 (3·43–10·02)	
Locoregional	11·36 (6·18–20·87)	
Metastatic	20·64 (11·92–35·75)	
Unclassifiable	6·49 (3·71–11·34)	

Values in parentheses are 95 per cent confidence intervals. Four patients without follow-up and one patient of unknown age were excluded. **P* for heterogeneity (likelihood ratio test)

preserving resection than larger tumours. The strongest factors relating to the choice of a continence-preserving resection were the location of the tumour in the upper part of the rectum (odds ratio 90·9) and the most recent study period (odds ratio 9·8). Neither age nor Dukes stage was associated with the choice of continence-preserving resection.

Among the 140 patients who underwent either a Hartmann procedure, an anterior resection or a coloanal anastomosis for cure, distal margins were compared before and after 1985. The percentage of distal margins inferior to 20 mm changed over time: 14 of 65 (22 per cent) in 1976–1985 and 38 of 79 (48 per cent) in 1986–1990 ($P<0·001$). The mean(s.d.) distal margins were 26(14) and 19(15) mm respectively ($P<0·001$).

Trends in operative mortality rate after surgery for cure

The overall operative mortality rate was 8·0 per cent (38 of 477). It increased with age: 3·6 per cent in patients aged less than 65 years (six of 166), 9·4 per cent in those aged between 65 and 74 years (15 of 159) and 11·2 per cent in those older than 74 years (17 of 152) (*P* for trend < 0·05). The operative mortality rate decreased from 13·9 per cent (22 of 158) in 1976–1980, to 6·3 per cent (ten of 159) in 1981–1985 and 3·8 per cent (six of 160) in 1986–1990 (*P* for trend < 0·001). These results were confirmed in the multivariate analysis (*Table 3*). There was almost a fourfold diminution of postoperative mortality rate between the first and the last 5-year periods. Age was also a significant prognostic factor. Sex, stage at time of operation, tumour location or tumour size had no influence on postoperative mortality rate.

Trends in survival

The overall 5-year crude survival rate was 32·7(s.e. 1·7) per cent, the corresponding relative survival rate being 42·9 per cent. Based on the age of the patient at the time of operation, the 5-year crude survival rate was 46·1(3·3) per cent for patients aged less than 65 years, 37(3·1) per cent for those aged between 65 and 74 years and 20·1 (2·2) per cent for those aged over 74 years (*P* for trend < 0·001). The corresponding relative survival rates were 49·7, 46·2 and 32·4 per cent respectively. The 5-year crude survival rate increased from 25·8(2·5) per cent in 1976–1980 to 31·8 (2·8) per cent in 1981–1985 and 42·6(3·3) per cent in 1986–1990 (*P* for trend < 0·001). The corresponding relative survival rates were 34·5, 42·0 and 56·0 per cent. This improvement with period of diagnosis was confirmed when a multivariate relative survival model was fitted (*Table 4*). Other prognostic factors were age and stage at operation. A similar increase in relative survival rate was found for the 1986–1990 period when analysing patients resected for cure separately ($n=477$): in comparison to 1976–1980 (baseline), survival increased with time for 1981–1985 (relative risk (RR) 0·96 (95 per cent confidence interval (c.i.) 0·66–1·37)) and for 1986–1990 (RR 0·59 (95 per cent c.i. 0·40–0·88)) (*P* for heterogeneity < 0·02).

Discussion

This study regarding time trends in the treatment, stage at operation and survival after diagnosis of carcinoma of the rectum has the advantage of including all cases diagnosed in a well defined French population of half a million inhabitants during the period 1976–1990. This study was therefore carried out without selection bias.

The percentage of favourable stages (Dukes A and B) rose from 35·8 to 52·5 per cent between the first and the last 5-year period. Various non-exclusive explanations may be found) including earlier first consultation, more rapid evaluation and increasing use of colonoscopy, suggesting a change of diagnosis strategy. As a consequence, the proportion of cancers treated for cure increased from 57 to 77 per cent. In contrast, palliative and non-operative treatments decreased by 10 per cent each.

The rate of continence-preserving resection in patients undergoing curative procedures was far greater during the last period studied (1986–1990) than during the first two 5-year periods while distal clearance of the specimen was decreasing. During the 1980s, several authors have produced data suggesting that a 5-cm margin was too stringent a requirement in cases of anterior resection and Hartmann procedures[12–14]. More recent publications have indicated that a distal clearance of 1 cm below the rectal tumour in an unfixed and unpinned specimen may be an adequate clearance in most instances[15,16]. In the present study, the percentage of distal margins less than 20 mm did change over time and this may have influenced the choice of a sphincter-saving procedure. The increasing percentage of short distal margins in the second part of the study may appear to be a dangerous trend. Nevertheless, one may note that all rectal specimens were measured unpinned and unfixed. It is therefore very difficult to compare techniques of length measurement between this population and those in specialized centres where specimens are received without delay from the operating theatre and are pinned under tension on a cork board[13,17]. In practice, with time, this shortening led to more frequent low anastomosis facilitated by the use of circular endoluminal staplers[5] which became readily available in France in 1978 but have been widely used only since 1985.

Cases of sphincter preservation with tumours below 8 cm from the anus were rare throughout the study and it appears that at a population level, coloanal anastomosis was rarely performed. This technique has not been widely adopted.

Despite the increase of continence-preserving resections, the value of 48 per cent during 1986–1990 may seem very low when compared with the value of 80 per cent in other institutional reports[5]. This referral bias is well known in the Calvados region where the percentage of continence-preserving resections increased from 25 to 45 per cent in specialized centres but only from 23 to 25 per cent in other institutions between 1978 and 1986[7]. In 1987, a survey from the French Association of Surgeons showed a rate of 41 per cent[18]. In 1965, the rate of continence-preserving resection was 28 per cent in Finland[19] and 28 per cent in the West Midlands from 1957 to 1981 among 23 534 cases of rectal cancer including the sigmoid junction[4].

Besides the time period and the level of the tumour in the rectum, other factors influenced the choice of a sphincter-saving procedure. Pelvic anatomy facilitated low colorectal anastomosis in women, and therefore a higher conservation rate of the anal sphincter. The tumour size was also a significant factor: large tumours required more extensive resection and did not facilitate continence-preserving resection. It is noteworthy that neither age nor Dukes stage was associated with the choice of a continence-preserving resection.

The improvement in survival remained significant after adjustment for age, sex and Dukes stage. The 5-year crude survival rate was 32·7 per cent but the improvement with time was significant; the survival rate was 42·6 per cent at the end of the study. The decrease in operative mortality rate after operation, from 13·9 per cent at the beginning of the study to 3·8 per cent in the last 5-year period, contributed to the improved survival. The sharp increase in the proportion of cancers limited to the rectal wall (Dukes A and B) is another factor. Nevertheless, the 5-year relative survival rate decreased with age even when using a relative multivariate model taking into account deaths in the Côte-d'Or population. Compared with all institutional results, this survival rate seems low but is comparable to data from other international population-based series. In a cooperative study of European registries, the 5-year crude survival rate for rectal cancer, including the rectosigmoid junction, was 28 per cent for 1976–1980 and 32 per cent for 1983–1985[3].

In conclusion, this study demonstrates that significant progress benefited the whole population in the management of rectal carcinoma in terms of survival and sphincter preservation. It also shows to the surgical community the difference in results between specialized centres and regional healthcare systems.

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Announcement

Trainees in coloproctology

The Inaugural Meeting of a Club for Trainees in Coloproctology from Great Britain and Ireland was held on 18 June 1997 at the ECCP Meeting in Edinburgh. The aims of the Club are to promote the interchange of information and ideas concerning training and research in coloproctology. Membership is free and all surgical trainees who have a declared specialist or subspecialist interest in coloproctology are eligible to join.

Sixty trainees attended the Inaugural Meeting which agreed a Club constitution and elected the following officers:

President:	John Stebbing (Bristol)
Secretary:	Tim Cook (oxford)
Trainee Representatives:	Mark Chapman (Nottingham)
	Eric Drabble (Cambridge)
	Stefan Plusa (Newcastle)

Those trainees wishing to register for membership and thereby receive details of Club activities should write to:

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Bone assessment in patients with ileal pouch–anal anastomosis for inflammatory bowel disease

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Background Patients with ulcerative colitis are at risk of low bone mineral density (BMD). Proctocolectomy with ileal pouch–anal anastomosis (IPAA) for ulcerative colitis diminishes the risk of bone disease. The aims of this study were to assess the mechanism of low BMD and to measure bone density changes after IPAA.

Methods Twenty patients with IPAA for ulcerative colitis, of mean(s.d.) age 38(9) (range 21–58) years, had measurements of lumbar spine and femoral neck BMD by dual energy X-ray absorptiometry, a mean(s.d.) 28(23) (range 3–84) months after proctocolectomy. Serum levels of calcium, phosphate, parathyroid hormone, osteocalcin and 25-hydroxy vitamin D were determined. Fifteen patients were followed for 28(12) (range 8–50) months.

Results At baseline, six patients had spine BMD more than two standard deviations below the normal value, and three had vertebral crush fractures. Mean vitamin D values were normal and no patient had osteomalacia. BMD increased with time elapsed since IPAA (spine: $r = 0{\cdot}71$, $P = 0{\cdot}005$). During follow-up, mean(s.d.) changes in bone density were +2·3(3·8) and +2·1(5·6) per cent per year at the spine and femoral neck respectively.

Conclusion These results suggest that in patients with IPAA for ulcerative colitis, low BMD is not associated with vitamin D malabsorption and may be reversible after surgery.

Abdominal colectomy with ileal pouch–anal anastomosis (IPAA) has become the surgical treatment of choice for most patients with uncontrolled ulcerative colitis. These patients have usually had very active inflammatory disease and a high dose of corticosteroids. Thus they are at high risk of low bone mineral density (BMD) and osteoporosis[1–7]. Increased rates of bone loss have also been reported in patients with inflammatory bowel disease (IBD) in prospective studies[8–11]. Low BMD is a relevant risk factor for osteoporotic fractures[12]. Proctocolectomy with IPAA, which removes all of the diseased mucosa, diminishes the risk of bone disease. The aims of this prospective study in patients with IPAA for ulcerative colitis were to assess the prevalence of low BMD, to assess changes in calcium-regulating hormones, and to measure BMD changes during follow-up.

Patients and methods

Patients

Consecutive patients who had undergone proctocolectomy with IPAA for ulcerative colitis were asked to take part in this longitudinal study. At baseline, clinical assessment included duration of the disease, time elapsed since IPAA, clinical nutritional status[13], body mass index (weight/(height)^2) and dietary inquiry[14]. In women hormonal status was assessed clinically by menstrual history. Cumulative lifetime steroid dose was expressed in grams of prednisone. Other therapies were documented. Anteroposterior and lateral radiographs of the thoracic and lumbar spine were reviewed at baseline only. The clinical assessment and measurements of weight variations (%) were repeated at the end of follow-up

Bone mineral density and radiological assessment

At baseline, BMD assessment was performed within a week after the clinical and biological assessments. BMD was measured by dual energy X-ray absorptiometry (Hologic QDR 1000, Waltham, Massachusetts, USA) at the lumbar spine (L2, L3, L4; posteroanterior view) and the femoral neck. BMD results were expressed as the number of standard deviations from normal values corrected for age and sex (Z score). All scans were performed by the same observer, with strict standardized positioning of the patients. For each patient, the scans were analysed at the same region of interest. During follow-up, percentage change in BMD was plotted to a mean annual variation. Short-term precision of the lumbar spine and femoral neck BMD measurements in young subjects are 1·0 and 1·2 per cent respectively. Thus, at the individual level, a BMD variation of at least 2·8 and 3·3 per cent at the lumbar spine and femoral neck respectively was considered statistically significant[15].

Biochemical assessment

Biochemical assessment was performed at baseline only. Serum concentrations of calcium, phosphorus, alkaline phosphatases and serum albumin, and sedimentation rate were measured by standard methods. Ionized calcium measurements were corrected automatically at pH 7·4 (ICA2 Radiometer). Total parathyroid hormone (PTH 1-84) was measured by a commercially available two-site immunoradiometric assay (Intact PTH; Nichols Institute, San Juan Capistrano, California, USA)[16]. Osteocalcin was measured by radioimmunoassay (Osteocalcin ^{125}I RIA Incstar; Incstar Corporation, Stillwater, Minnesota, USA). Serum 25-hydroxy vitamin D concentrations were measured by a competitive protein binding assay after extraction and chromatographic purification; the coefficient of variation for this method was 9 per cent for low and normal values[17].

Statistical analysis

Results were expressed as mean(s.d.) (range). Linear regression analysis and the Spearman's rank correlation test were used as

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appropriate. In all statistical analysis $P<0\cdot05$ was considered significant.

Results

Patients

Twenty consecutive patients with IPAA after ulcerative colitis (nine women), aged 38(9) (range 21–58) years, participated in the study. Proctocolectomy and IPAA had been performed 28(23) (range 3–84) months before the study. Duration of the disease was 61(6) (range 2–219) months at the time of proctocolectomy. Four patients had never received steroid therapy. In the remaining patients, the cumulative lifetime steroid dose was 8·5(6·4) (range 0·4–21·5) g. Eight patients had pouchitis, with endoscopic lesions in the reservoir. At baseline, the clinical nutrition status was normal in all except one patient who had clinical signs of malnutrition. Body mass index was 21·4(3·1) (range 15–30) kg/m^2. Total calorific intake was 2376(752) (range 1000–3700) kcal/day; protein, fat and carbohydrate oral intake was 16, 34 and 50 per cent of the total calorific intake respectively. Calcium intake was 760(260) (range 400–1400) mg/day. All the women had regular menses except for a 34-year-old woman who had had amenorrhoea for 4 years. No patient had bone or muscular pain or was bedridden at the time of evaluation. Fifteen patients were followed for 28(12) (range 8–50) months. During follow-up, all patients remained in clinical remission and did not receive steroids. Change in weight was 7·1(7·2) (range −5 to +19) per cent.

Biochemical assessment

At baseline, no patient had an inflammatory syndrome or low serum albumin level (*Table 1*). Biochemical markers of bone metabolism were normal, except serum osteocalcin which was below 2 ng/ml in six patients. One patient had a serum vitamin D level below normal because of malnutrition and lack of sunshine exposure. One patient had a high osteocalcin value with no abnormality of calcium-regulating hormones. No patient showed secondary hyperparathyroidism. There was no difference in 25-hydroxy vitamin D levels according to the presence or absence of pouchitis (data not shown).

Table 1 Serum measurements in 20 patients with ileal pouch–anal anastomosis after ulcerative colitis

	Normal range	Patients with IPAA*
Sedimentation rate (mm/h)		19(6) (3–31)
Albumin (g/l)	35–45	41·2(6·6) (37–46)
Calcium (mmol/l)	2·2–2·6	2·3(0·1) (2·1–2·5)
Phosphorus (mmol/l)	0·8–1·5	1·15(0·15) (0·9–1·4)
Alkaline phosphatase (units/l)	<90	58·3(14·4) (39–92)
Osteocalcin (ng/ml)	2–7	4·2(4·8) (0·6–16)
25-Hydroxy vitamin D (ng/ml)	5–30	12·2(6·4) (2·2–27)
Parathyroid hormone (1–84) (pg/ml)	10–60	28(10) (16–55)

*Values are mean(s.d.) (range) serum level. IPAA, ileal pouch–anal anastomosis

Bone mineral density measurements and radiological assessments

Radiography revealed vertebral crush fractures in three patients (two women and one man; mean age 40 years). Z scores at baseline were −1·6(1·5) (range −5·1 to +0·8) and −1(1·2) (range −3·7 to +0·8) respectively at lumbar spine and femoral neck levels. Eleven patients had Z scores more than one standard deviation below normal and in six the scores were more than two standard deviations below normal at the spine. There was a positive correlation between lumbar spine or femoral neck Z score and the time elapsed since proctocolectomy ($r=0\cdot71$, $P=0\cdot005$ and $r=0\cdot63$, $P=0\cdot004$ respectively) (*Fig. 1*). In patients who had previously received corticosteroids ($n=16$), there was no correlation between cumulative prednisone dose and lumbar or femoral BMD. During follow-up, annual BMD changes were +2·3(3·8) (range −1·9 to +12) and +2·1(5·6) (range −5·6 to +14·5) per cent at the lumbar spine and femoral neck respectively. There was a correlation between the spine BMD change and duration of follow-up, which approached significance ($r=+0\cdot47$, $P=0\cdot07$) (*Fig. 2*). For the whole follow-up period, statistically significant bone loss was observed in one and four patients at the lumbar spine and femoral neck levels respectively, including the patient with long-duration amenorrhoea. An individual significant increase in BMD was observed in seven patients at the lumbar spine (*Fig. 2*) and at the femoral neck. The changes between lumbar and femoral BMD were correlated ($r=+0\cdot86$, $P<0\cdot0001$). There was no correlation between changes in BMD and in weight.

Discussion

These data suggest that patients who undergo IPAA for ulcerative colitis are at high risk of low BMD and vertebral crush fractures. This low BMD is not associated

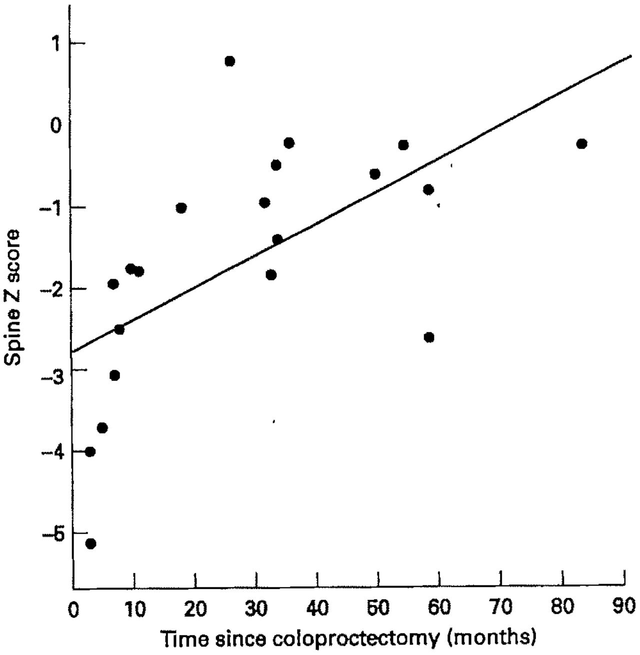

Fig. 1 Spine bone mineral density, expressed as Z score, as a function of time since coloproctectomy

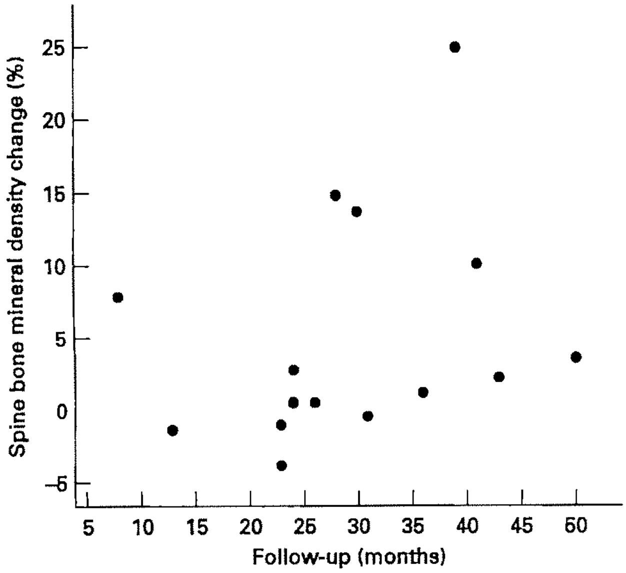

Fig. 2 Percentage spine bone mineral density changes during follow-up in 15 patients after ileal pouch–anal anastomosis for ulcerative colitis

with vitamin D malabsorption, and may be reversible after surgery.

The most frequent long-term complication after IPAA for ulcerative colitis is a non-specific inflammation of the ileal reservoir or pouchitis[18,19]. Eight patients in this study had endoscopic and histological signs of pouchitis. None of them had fever, extraintestinal manifestations or biochemical inflammatory syndrome.

At baseline, these patients had a high prevalence of low BMD at spinal and femoral levels, and vertebral crush fractures occurred in three of them. In previous cross-sectional studies, low BMD and vertebral crush fractures have been reported in 31–59 per cent[1–7] and 7 per cent[1,2] respectively of patients with IBD. Among patients with IBD, those at greatest risk of osteoporosis are young patients with a high corticosteroid requirement and a high sedimentation rate, and who have an inflammatory syndrome[1]. The high prevalence of low BMD in this study may be explained by this pre-existing inflammatory syndrome in patients who had been treated for ulcerative colitis and/or received a high cumulative steroid dose before surgery. Confinement to bed in the perioperative period may also have increased the bone loss.

Osteoporosis in patients with IBD results from low bone turnover[20,21] as expressed by low osteocalcin levels, in the presence of normal levels of calcium-regulating hormones[1]. After IPAA for ulcerative colitis, bacterial overgrowth is a constant finding in the pouch, which could be the consequence of faecal stasis and bacterial colonization of the reservoir[22,23]. Bacterial overgrowth in the ileal pouch may lead to deconjugation of bile acids and thus impaired reabsorption of bile acids[23,24]. This is a theoretical cause of malabsorption of vitamin D[25]. However, all but one of the present patients had normal levels of 25-hydroxy vitamin D. Since 25-hydroxy vitamin D plays a prominent role in the regulation of calcium absorption[26], and these patients had normal levels of calcium-regulating hormones, it may be speculated that they had normal calcium absorption No patient had clinical signs of osteomalacia or secondary hyperparathyroidism.

Prospective studies have shown an increased rate of bone loss in patients with IBD[8–11], especially in patients with ulcerative colitis (6·4 per cent per year)[11]. On average, patients with IPAA, cured of the inflammatory disease and not receiving corticosteroid therapy, had no further decrease of spine BMD. BMD increased with the time elapsed since proctocolectomy, and a spontaneous individual significant increase in lumbar BMD was observed in seven patients during follow-up. Recovery of bone density has also been reported among women with primary biliary cirrhosis after liver transplantation[27] and in patients with Cushing syndrome after surgery[28,29].

In conclusion, low BMD and vertebral crush fractures in patients with IPAA for ulcerative colitis are not associated with vitamin D malabsorption. After IPAA, a spontaneous increase in bone mineral density is seen.

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Magnetic resonance imaging of the pelvic floor in patients with obstructed defaecation

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Background Evacuation proctography and measurements of anorectal physiology are frequently used to clarify the pathophysiology of obstructed defaecation. In some patients these tests are normal, despite convincing clinical evidence of defaecatory difficulty. The aim of this study was to determine whether magnetic resonance imaging (MRI) could reveal pelvic floor abnormality in patients with obstructed defaecation.

Methods Eleven women with obstructed defaecation, in whom evacuation proctography and anorectal physiology were normal, were examined by MRI, using a fast gradient echo sequence. Measurements of pelvic visceral and muscular descent were taken at rest and during straining, and compared with those obtained from 13 asymptomatic volunteers.

Results Patients with obstructed defaecation had significantly greater pelvic visceral descent ($P < 0{\cdot}05$), levator muscle descent ($P = 0{\cdot}04$), levator plate angle change ($P = 0{\cdot}003$) and increase in the area of the pelvic floor hiatus ($P = 0{\cdot}0002$) than asymptomatic volunteers.

Conclusion MRI demonstrated marked pelvic visceral and levator muscle descent in women with obstructed defaecation, despite normal evacuation proctography and anorectal physiology. MRI should be considered if these examinations have been normal.

Obstructed defaecation is defined as an inability to initiate defaecation, a feeling of incomplete evacuation or excessive straining at stool. It may result from a variety of causes, including mechanical derangement such as intussusception[1] and rectocele[2], or inappropriate pelvic floor contraction during defaecation, a condition usually termed anismus[3,4].

Evacuation proctography and measurements of anorectal physiology are frequently used to clarify the pathophysiology of obstructed defaecation[1,2,4,5]. Despite convincing clinical evidence of defaecatory difficulty, these tests are normal in some patients[6,7]. Recently, magnetic resonance imaging (MRI) has been used to demonstrate pelvic visceral prolapse and anorectal configuration[8–11].

This study aimed to show whether MRI could diagnose pelvic floor abnormalities in patients with obstructed defaecation.

Patients and methods

Eleven women of median age 62 (range 38–82) years who presented with straining at stool, a feeling of incomplete rectal emptying and perineal digital manipulation to aid evacuation were studied. All had normal evacuation proctography and anorectal physiology tests.

Thirteen asymptomatic female volunteers (median age 53 (range 30–71) years also had MRI. Volunteers were assessed by a detailed questionnaire and history taken by a coloproctological surgeon[12]. There was no significant difference for age or parity between patients and volunteers.

This study had ethics committee approval and all subjects gave informed written consent.

Imaging technique and analysis

MRI was performed on a 1·5-T unit (Signa; GE Medical Systems, Milwaukee, Wisconsin, USA). Soft tubes (5 mm diameter) were placed in the vagina and rectum as luminal markers. Images were obtained with the patient supine at rest and during straining, to simulate evacuation, in the sagittal, coronal and axial planes using a fast spoiled gradient recalled acquisition in a steady state sequence (flip angle 30°; repetition time (TR)/echo time (TE) 11·6/4·2; field of view 34 cm; slice thickness 7 mm, interslice gap 2 mm; matrix size 256 × 128; two excitations).

The position of the bladder base, uterocervical and anorectal junctions were measured at rest and during straining in relation to the pubococcygeal line (a line joining the pubic symphysis and the last coccygeal joint)[8–11].

The anorectal angle, defined as the angle formed by the longitudinal axis of the anal canal and the posterior rectal wall[1,7] was measured at rest and during straining, and its change calculated. The development of acute angulation on straining was also noted

The levator plate angle, defined as the angle between the pubococcygeal line and the levator plate was measured at rest and during straining, and its change calculated[13].

The 'pelvic floor hiatus' cross-sectional area, defined as the area enclosed by the pelvic floor muscles through which pass the urethra, vagina and anal canal, was measured at the level of the symphysis pubis at rest and during straining[11].

Measurements of the surface area of the levator muscles at rest and during straining were calculated from dimensions taken from coronal images, assuming that the levator muscle configuration resembled a truncated cone.

Statistical analysis

Patients with obstructed defaecation were compared with volunteers for continuous variables using the Mann–Whitney *U* two-sample test for unpaired non-parametric data. Non-continuous tabular data were analysed using Fisher's exact test. Statistical significance was attributed at the 5 per cent level. (Instat version 2 05, Graph Pad, San Diego, California, USA)

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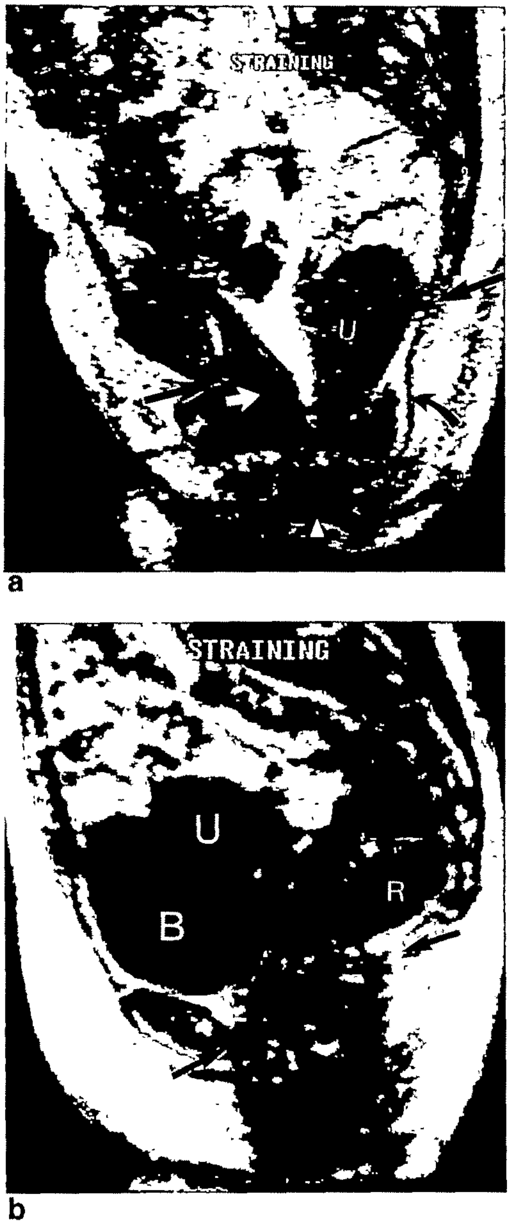

Fig. 1 a Sagittal magnetic resonance image of a 46-year-old woman with obstructed defaecation during straining shows marked descent of the bladder (white arrow), uterus (U) and rectum (arrowhead) below the pubococcygeal line (straight black arrows). Note the marked descent of levator plate (curved arrow) posteriorly b Sagittal image of a 37-year-old asymptomatic female volunteer during straining shows the bladder (B), uterus (U) and rectum (R) above the pubococcygeal line (arrows)

Results

Dynamic MRI was easy to perform and well tolerated, with an average examination time of 20 min.

No significant difference was found between patients or volunteers for the position of the bladder base, uterocervical or anorectal junctions at rest. However, during straining, the position of these organs was significantly lower in patients than in volunteers (*Table 1*, *Figs 1a* and *1b*)

Patients had a significant increase in levator plate angle during straining compared with volunteers (*Table 2*).

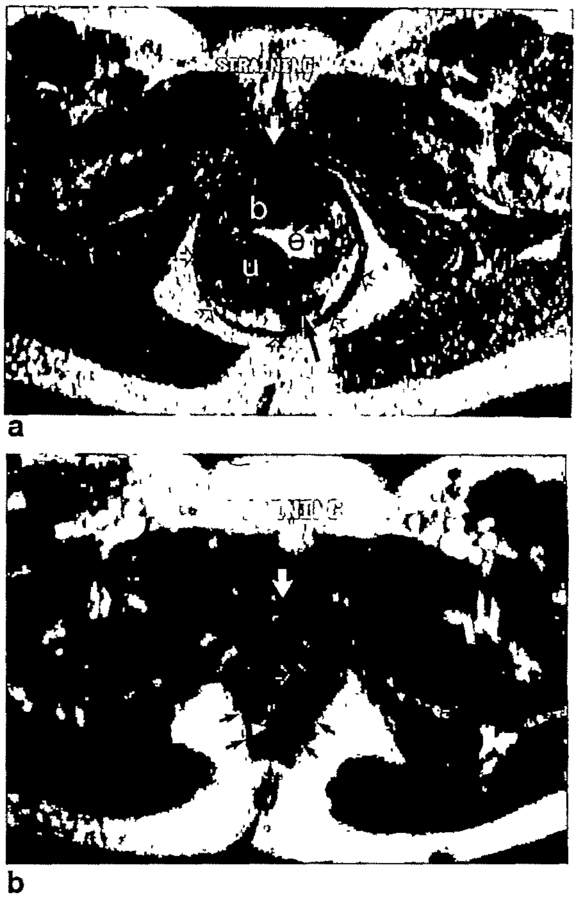

Fig. 2 a Axial magnetic resonance image of a 46-year-old woman with obstructed defaecation at the level of the pubic symphysis (closed white arrow) during straining shows marked ballooning of the puborectalis muscles (open arrows), with descent of the bladder (b), enterocele (e), uterus (u) and rectum (black arrow) b Axial image of a 37-year-old asymptomatic female volunteer during straining shows a tube in the vagina (open arrow) and anal canal (arrowhead) with no ballooning of the puborectalis muscles (black arrows)

No significant difference was found between patients and volunteers in the size of the anorectal angle at rest, during straining or for the magnitude of its change. However, the anorectal angle became more acute during straining in eight of 11 patients, but in only three of 13 volunteers ($P = 0{\cdot}04$).

The area of the pelvic floor hiatus and levator muscle surface area was not significantly different between patients and volunteers at rest (*Table 3*). However, patients had a significantly larger pelvic floor hiatus and levator muscle surface area during straining than volunteers (*Table 3*, *Figs 2a* and *2b*).

Discussion

The aetiology of obstructed defaecation is complex, and may include anatomical and/or functional causes[14]. Evacuation proctography will diagnose structural rectal abnormality and suggest functional abnormality when contrast evacuation is slow or incomplete[5]. Anorectal physiology measurement may diagnose abnormalities of pelvic musculature and nervous innervation. However, as

Table 1 Position of pelvic viscera at rest and during straining

	Position with respect to pubococcygeal line (mm)		
	Constipated patients ($n = 11$)	Asymptomatic volunteers ($n = 13$)	P*
Bladder base			
Resting	14 (0 to 32)	15 (6 to 25)	0·75
Straining	−25 (−50 to 0)	−7 (−32 to 19)	0·03
Uterocervical junction			
Resting	21 (0 to 39)	18 (9 to 34)	0·68
Straining	−26 (−58 to 0)	0 (−33 to 20)	0·007
Anorectal junction			
Resting	−11 (−26 to 13)	0 (−18 to 18)	0·07
Straining	−41 (−80 to −24)	−14 (−55 to 13)	0·002

Values are median (range). *Mann–Whitney U test

Table 2 Anorectal angle and levator plate angle at rest and during straining

	Angle (°)		
	Constipated patients ($n = 11$)	Asymptomatic volunteers ($n = 13$)	P*
Anorectal angle			
Resting	115 (107 to 125)	110 (85 to 126)	0·10
Straining	102 (48 to 149)	118 (78 to 142)	0·40
Change	−12 (−77 to 32)	8 (−29 to 28)	0·12
Levator plate angle			
Resting	0 (0 to 20)	12 (0 to 44)	0·12
Straining	45 (38 to 73)	22 (6 to 70)	0·08
Change	45 (18 to 68)	8 (3 to 58)	0·003

Values are median (range). *Mann–Whitney U test

Table 3 Magnetic resonance imaging measurement of the pelvic floor muscles at rest and during straining

	Constipated patients ($n = 11$)	Asymptomatic volunteers ($n = 13$)	P*
Pelvic floor hiatus (cm^2)			
Resting	2208 (1804–3074)	2119 (1536–3001)	0·09
Straining	6051 (3709–7209)	2773 (1584–5343)	0·0002
Surface area of levator ani (cm^2)			
Resting	2092 (1010–3431)	2088 (1209–2944)	0·60
Straining	4246 (2206–9002)	2833 (1704–5163)	0·04

Values are median (range). *Mann–Whitney U test

in this study, some patients may not demonstrate convincing abnormality on these standard investigations[7].

MRI during straining reveals striking differences in pelvic floor configuration between patients and volunteers. The patients had marked pelvic floor ballooning and consequently visceral prolapse. This suggests muscular weakness and lack of adequate anatomical support, which was not identified on standard evacuation proctography or by anorectal physiology measurement.

The significantly larger levator muscle surface area in patients during straining, which was used to describe the marked descent of the levator muscles seen in the coronal plane on MRI (*Figs 3a* and *3b*), suggests that these patients appear to have marked lengthening of these muscles during straining. The levator descent and pelvic floor ballooning may be related to a neuropathy which was not apparent on standard anorectal physiology testing. During anorectal physiology the terminal motor latency of the pudendal nerve (S2,3,4) is measured, not the supply to the levator muscles, which is from perineal branches of S3,4,5 directly entering the muscles from above.

Descent of the levator plate posterior to the anorectal junction during straining was pronounced in the constipated patients. In anismus, evacuation proctography demonstrates persistent or accentuated puborectal impression posterior to the anorectal junction, consistent with paradoxical levator plate contraction, which supports the rectum and opposes raised intra-abdominal pressure[15,16]. Contraction of the levator plate was not seen on MRI suggesting that the patients studied are different from those with anismus. Acute angulation of the anorectal angle was frequently seen on MRI in these patients, due to the marked pelvic floor descent and ballooning. In anismus increased puborectalis muscle activity would be expected to produce narrowing of the pelvic floor hiatus[16].

The pelvic visceral prolapse demonstrated in this study by MRI is strongly associated with difficulty in defaecation[10,14,17]. It remains uncertain whether these findings are the primary cause of defaecatory difficulty, following laceration or neuropathy sustained during previous vaginal birth, or whether they are merely a consequence of prolonged straining at stool, secondary to a pre-existing functional disorder of unknown cause[17]. The feelings of incomplete evacuation experienced by these patients may be a consequence of prominent pelvic visceral prolapse simulating the sensation of a full rectum, rather than an inability to evacuate the rectum. This is likely as all had a normal evacuation proctography profile. The sensation of rectal fullness may be derived from nerves which lie outside the rectum, in the pelvic floor musculature[18]. It is controversial whether surgical repair of the sites of pelvic floor weakness and prolapse might be a suitable treatment for this group of patients.

At present, MRI is less physiological than proctography as it is performed with the patient supine, and involves straining and not rectal evacuation. Additionally, evacuation proctography shows the completeness and speed of evacuation and also images mucosal abnormalities such as rectal intussusception, rectal prolapse and solitary rectal ulcer, which may be treated surgically[5]. However MRI has demonstrated pelvic floor descent with marked muscle ballooning and visceral prolapse in patients with obstructed defaecation who had no abnormalities on standard investigations. The benefits of MRI include: multiplanar capability, non-invasiveness, speed, and avoidance of ionizing radiation. MRI should be considered for evaluation in patients with convincing clinical features of defaecatory difficulty, who have had normal evacuation proctography and anorectal physiology measurements.

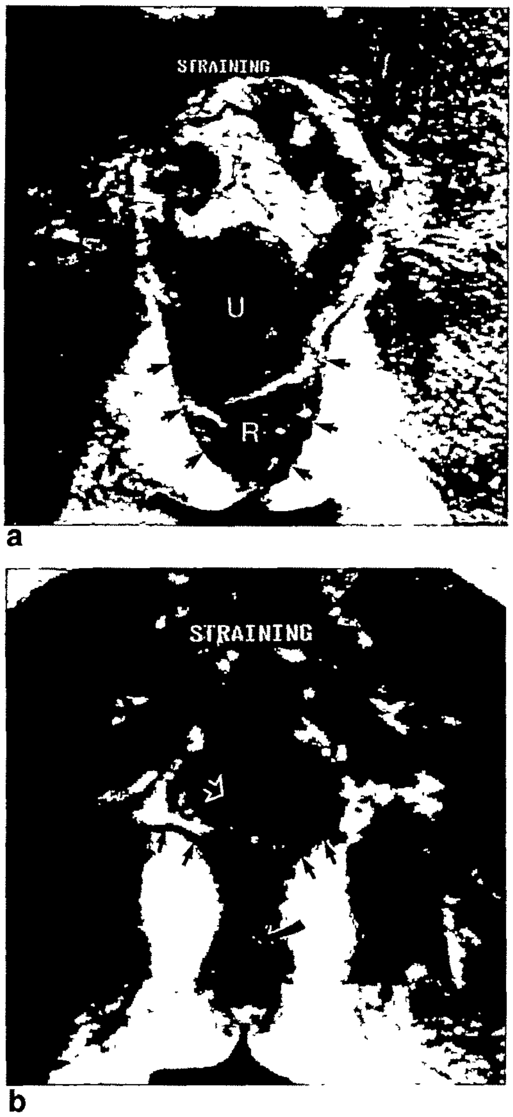

Fig. 3 a Coronal magnetic resonance image of a 46-year-old woman with obstructed defaecation during straining shows marked descent and lengthening of levator muscles (arrows) with consequent descent of the uterus (U) and rectum (R). b Coronal image of a 37-year-old asymptomatic female volunteer during straining shows a tube in the anal canal (curved black arrow). Levator muscles (black arrows) have not descended significantly and the rectum (open arrow) remains above the pelvic floor during straining

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Tumour bed positivity predicts outcome after breast-conserving surgery

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Background Local recurrence after breast-conserving surgery is associated with a short distant disease-free survival, particularly if it occurs early. Early local recurrence is caused by residual disease left at the time of surgery. Previous studies have demonstrated that disease in the tumour bed is a common finding after breast-conserving surgery.

Methods The follow-up (mean 4·4 years) of 300 patients who had tumour bed analysis performed by the cavity shaving technique following breast-conserving surgery is presented. Postoperative radiotherapy was administered to all patients.

Results The incidence of tumour bed positivity was 39·3 per cent. With a selective re-excision policy the local recurrence rate was 2·0 per cent and distant recurrence rate 10·4 per cent. Multivariate analysis identified lymphovascular invasion, oestrogen receptor status and tumour bed status as independent predictors of time to distant recurrence.

Conclusion A low rate of local recurrence can be achieved using this technique of margin assessment. Tumour bed status may be a useful prognostic factor following breast-conserving surgery.

Local recurrence after breast-conserving surgery is associated with a short distant disease-free survival. Patients with local recurrence are two to four times more likely to develop metastases than those without local recurrence and this risk increases sixfold if local recurrence occurs within 1 year of surgery[1–4]. Early local recurrence can be attributed to residual disease left at the time of surgery since nearly all recurrences occur at the site of previous excision and are histologically concordant with the primary tumour[5]. The evidence implicating local recurrence with the development of disseminated disease does not, however, translate into significant survival differences between the treatment arms in randomized trials[1,2,6,7]. Currently, the accepted explanation of the relationship between local recurrence and systemic recurrence is that local recurrence is a marker of poor prognosis rather than the cause of it[1].

Previous studies have reported that residual microscopic disease in the tumour bed is a common finding following breast-conserving surgery[8–10]. The purpose of this study was to correlate disease in the tumour bed with outcome and test the hypothesis that residual microscopic disease may be a marker of poor prognosis.

Patients and methods

Patients

Three hundred patients with invasive breast cancer entered the study between March 1988 and September 1992. Their mean age was 55·3 (range 27–81) years. Some 174 patients presented symptomatically and 126 were referred through the National Breast Screening Programme (69 with palpable lesions). All patients were followed up 3 monthly for the first 5 years at alternate surgical and oncology clinics, and 6 monthly thereafter.

Surgical management

A wide local excision was performed with a 1–2-cm macroscopic margin. The deep extent of excision was the pectoral fascia. Tissue forceps were then applied to the breast tissue lining the wall of the cavity and this was excised completely and submitted separately for histopathology labelled ‘cavity shaving’[10]. An axillary clearance was performed for nodal staging.

Pathological assessment

The maximum diameter of the tumour and presence of tumour within lymphatic or vascular channels (lymphovascular invasion) was recorded. Tumours were graded using the Bloom and Richardson grading system[11]

The total number of blocks for the cavity shavings ranged between 20 and 40 depending on the specimen volume All blocks were sectioned serially and the type and extent of disease assessed[10]. Tumours were immunohistochemically stained for oestrogen receptor status.

Statistical analysis

Patients were analysed with regard to disease-free, distant disease-free and overall survival. Univariate analyses were performed using Kaplan–Meier techniques for estimation of the survival curves and the log rank test for comparison of different patient subgroups. The subgroups analysed were patient age, tumour grade, tumour size, nodal status, presence of lymphovascular invasion, oestrogen receptor status and tumour bed status For continuous measurements the patients were split into groups defined by the quartiles of the measurements. Multivariate analyses were performed for distant disease-free survival using the Cox proportional hazards model[12] to allow assessment of the interrelationship between factors.

Results

Two patients were lost to follow-up and 298 patients were therefore evaluable. Mean follow-up was 4·4 (range 2·0–7·5) years. Preliminary results of this study, including analyses of tumour bed status relative to clinicopathological factors, have been published previously[10].

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Neoplasia was found in the cavity shavings of 118 of 300 patients (39·3 per cent). Residual invasive disease was found in 55 patients (18·3 per cent) and *in situ* disease with no invasive component in 63 patients (21·0 per cent). The extent of disease in the cavity shavings varied widely. Positivity ranged from one focus of ductal carcinoma *in situ* involving one block to extensive invasive disease involving several blocks. Based on the extent of disease identified in the cavity shavings, further surgery was performed in 41 patients. Criteria for re-excision have been described previously[10]. Eight patients had a further wide local excision and 33 patients underwent mastectomy. Of patients who underwent further surgery 22 had histological evidence of further residual disease.

All patients received postoperative radiotherapy to the breast. This consisted of 46 Gy in 23 fractions over 35 days with a 12-Gy boost to the site of excision in four fractions over 7 days using 6-mega electron voltage electrons. A total of 232 patients received tamoxifen and 18 patients received chemotherapy. The administration of adjuvant systemic therapy did not differ significantly relative to tumour bed status (*Table 1*).

Predictors of tumour bed positivity

There was a significant relationship between tumour bed positivity and high tumour grade ($P = 0{\cdot}02$). There was no significant association between tumour bed positivity and patient age ($P = 0{\cdot}08$), tumour size ($P = 0{\cdot}45$), node status ($P = 0{\cdot}83$), lymphovascular invasion ($P = 0{\cdot}63$) or oestrogen receptor status ($P = 0{\cdot}46$).

Site of recurrence

The site of first relapse is shown in *Table 2*. A total of 24 patients died from breast cancer and 11 from other causes.

Table 1 Number of patients who received adjuvant treatment relative to tumour bed status

Adjuvant treatment	No. of patients ($n = 300$)	Tumour bed status	
		Negative ($n = 182$)	Positive ($n = 118$)
Tamoxifen	232 (77·3)	139 (76·4)	93 (78·8)
Chemotherapy	18 (6·0)	12 (6·6)	6 (5·1)

Values in parentheses are percentages

Table 2 Frequency and first site of disease recurrence ($n = 298$)

Site of relapse	No. of recurrences
Ipsilateral breast	6 (2·0)
Ipsilateral axilla	2 (0·7)
Contralateral breast	4 (1·3)
Distant metastases	31 (10·4)

Values in parentheses are percentages

Predictors of time to development of distant disease

Variables were assessed individually as predictors of time to distant recurrence. All had significant or near-significant associations with distant recurrence (*Table 3*). The life-table analysis of tumour bed status in relation to distant disease is shown in *Fig. 1*.

Multivariate analysis was then performed. Lymphovascular invasion, oestrogen receptor status and tumour bed status were identified as a set of independently useful predictors of distant disease-free survival. After adjustment for these factors no other factors were significant. No statistically significant interactions were found between these factors in the final model. Life-table analyses of tumour bed status and presence of lymphovascular invasion or tumour bed status and oestrogen receptor status are shown in *Figs 2* and *3*. Patients with tumour bed positivity and either oestrogen receptor-negative tumours or tumours with lymphovascular invasion appeared to be at particular risk of distant disease.

Forty-one patients underwent further surgery because of extensive disease in the cavity shavings. There was no significant difference in outcome between those who were tumour bed positive and had further surgery and those who were tumour bed positive and had no further surgery (*Fig. 4*).

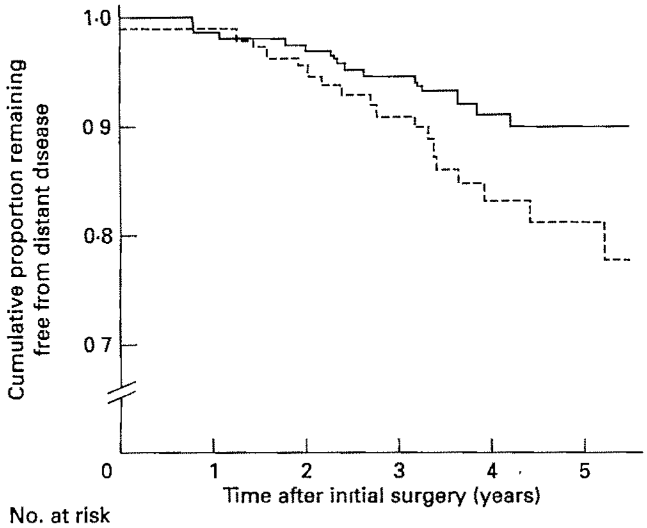
Discussion

This study has shown that neoplastic disease in the tumour bed is a common finding after breast-conserving surgery. The incidence of tumour bed positivity in this study (39·3 per cent) closely approximates that predicted by pathological studies on mastectomy specimens (43 per cent) and with the incidence of local recurrence in patients who do not receive radiotherapy (53 per cent at 9 years)[5,13]. In this study tumour bed positivity was associated with a shorter distant disease-free survival.

Table 3 Predictors of time to development of distant disease (univariate analysis)

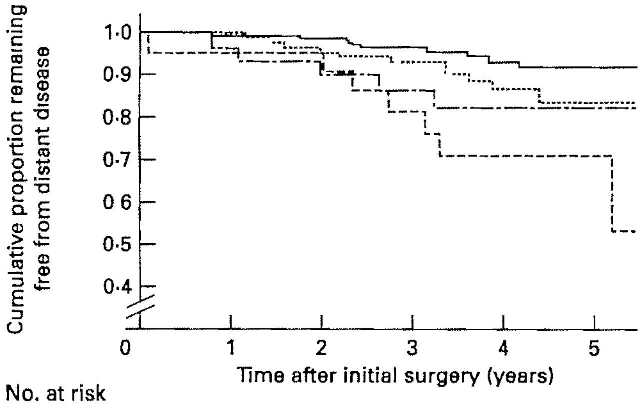
Variable	Comparison for relative hazard estimation	Relative hazard*	*P*†
Age	Upper quartile *versus* lower quartile	0·86 (0·57–1·31)	0·035
Tumour grade	2 *versus* 1	3·30 (0·95–11·5)	0·019
	3 *versus* 1	5·50 (1·45–20·9)	
	3 *versus* 2	1·66 (0·73–3·76)	
Tumour size	Upper quartile *versus* lower quartile	1·66 (1·08–2·54)	0·068
Node status	Positive *versus* negative	2·70 (1·25–5·83)	0·007
Lymphovascular invasion	Present *versus* absent	2·94 (1·44–6·01)	0·002
Oestrogen receptor status	Negative *versus* positive	2·26 (1·10–4·66)	0·020
Tumour bed status	Positive *versus* negative	2·03 (1·00–4·15)	0·042

*Point estimate for relative hazard with 95 per cent confidence intervals in parentheses. †Log rank test



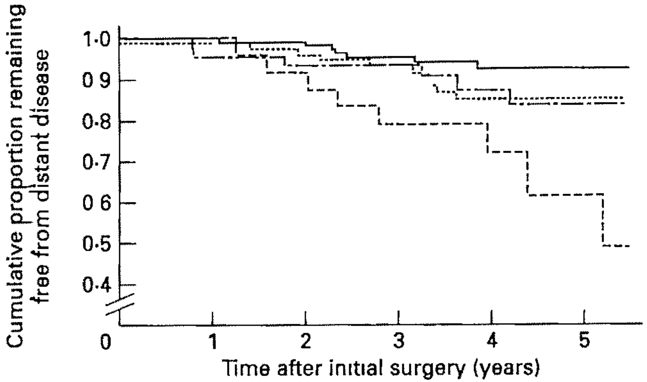
No. at risk					
Tumour bed –	178	175	134	87	47
Tumour bed +	116	110	79	50	28

Fig. 1 Proportion of patients remaining free from distant disease relative to tumour bed status. ———, Tumour bed negative; – – – –, tumour bed positive. $P = 0·042$ (log rank test)



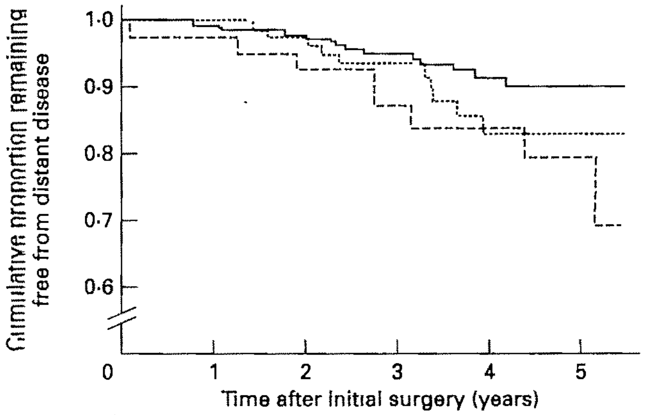
No. at risk					
Tumour bed –/no lymphovascular invasion	150	149	111	73	41
Tumour bed +/no lymphovascular invasion	95	90	63	42	24
Tumour bed –/ lymphovascular invasion	29	27	23	14	6
Tumour bed +/ lymphovascular invasion	21	21	16	10	7

Fig. 2 Proportion of patients remaining free from distant disease relative to tumour bed status and presence of lymphovascular invasion. ———, Tumour bed negative, no lymphovascular invasion; · ·, tumour bed positive, no lymphovascular invasion; –·–, tumour bed negative, with lymphovascular invasion; – – –, tumour bed positive, with lymphovascular invasion. $P = 0·002$ (log rank test)



No. at risk					
Tumour bed –/ oestrogen receptor +	115	113	86	55	35
Tumour bed +/ oestrogen receptor +	44	43	37	25	13
Tumour bed –/ oestrogen receptor –	83	80	57	38	22
Tumour bed +/ oestrogen receptor –	24	22	17	8	4

Fig. 3 Proportion of patients remaining free from distant disease relative to tumour bed status and oestrogen receptor status. ———, Tumour bed negative, oestrogen receptor positive; ··· ·, tumour bed positive, oestrogen receptor positive, –·–·–, tumour bed negative, oestrogen receptor negative; – – –, tumour bed positive, oestrogen receptor negative. $P = 0·004$ (log rank test)



No. at risk					
No further surgery/ tumour bed –	178	175	134	86	48
No further surgery/ tumour bed +	76	74	51	31	18
Further surgery	39	38	30	21	11

Fig. 4 Proportion of patients remaining free from disease relative to tumour bed status and further surgery. ———, Tumour bed negative, no further surgery; ····, tumour bed positive but no further surgery; – – –, further surgery. $P = 0·09$ (log rank test)

Patients with disease in the tumour bed were twice as likely to develop distant metastasis as those who were tumour bed negative. In addition tumour bed positivity, presence of lymphovascular invasion and oestrogen receptor status were found to be independent predictors of distant disease-free survival. Patients who were oestrogen receptor negative and tumour bed positive appeared to have a particularly high risk of distant metastasis with a distant disease-free survival rate of less than 50 per cent compared with greater than 90 per cent for patients who were oestrogen receptor positive and tumour bed negative (mean follow-up 4·4 (range 2·0–7·5) years).

Disease left at the time of breast-conserving surgery is the cause of local recurrence. The association between local recurrence and distant disease is well recognized. A Cox regression model analysis of local recurrence in the National Surgical Adjuvant Breast and Bowel Project (NSABP)-B06 trial demonstrated that patients who developed local recurrence after breast-conserving surgery were 3·41 times more likely to develop distant disease[1]. In addition, at 1-, 2- or 5-year cut-offs, patients who had early local relapse were significantly more likely to develop distant disease than those who experienced this event late. A similar analysis was performed on results from the Ontario Cancer Treatment and Research Foundation randomized trial of breast-conserving surgery with or without radiotherapy[2]. This showed that the relative risk of developing distant disease and overall mortality was more than doubled in patients who had local recurrence (2·11 and 2·18 respectively). Again, patients who developed local recurrence within 1 year were at significantly higher risk than those in whom local recurrence occurred late. Applied to data from the Milan breast conservation trials and a large group of non-randomized patients treated by quadrantectomy, the Cox regression model analysis has shown the risk for distant disease to be 4·62 times greater in patients who had a local recurrence. In this trial the risk was six times greater if local recurrence occurred within 1 year[3].

In the NSABP-B06 trial 10 per cent of patients had a positive resection margin determined by India ink staining and these patients all underwent mastectomy[6]. In this trial no significant difference in survival was found between patients who received breast-conserving surgery alone and those who also received adjuvant radiotherapy despite large differences in local recurrence rates. This led Fisher *et al.*[1] to suggest that local recurrence was a marker for distant disease rather than a cause of it[1]. In the present study 41 patients (13·6 per cent) underwent further surgery because of extensive disease involvement of the cavity shavings. The distant disease-free survival rate tended to be worse in patients who had further surgery (*Fig. 4*). This finding is consistent with the concept that no causal relationship exists between residual disease in the tumour bed and distant disease-free survival. The mechanism for the association between local recurrence and distant disease may be the same as that between tumour bed positivity and distant disease, and requires further investigation. Tumour bed analysis is a useful method of assessing completeness of surgical excision. A selective re-excision policy for cavity shaving positivity results in a low local recurrence rate. This study has also demonstrated that tumour bed status is a marker for distant disease-free survival.

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Pathological appearance of the stomach after endoscopic mucosal resection for early gastric cancer

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Background The pathological findings of the resected stomach after endoscopic mucosal resection (EMR) for early gastric cancer were reviewed EMR was indicated when a lesion consisting of well or moderately differentiated adenocarcinoma had a diameter of less than 2 cm.

Methods Of 39 patients with early gastric cancer who were treated with EMR between 1990 and 1995, 11 required additional surgery.

Results Malignant tissue in the gastric wall was completely removed in four patients, while cancer cells remained in the mucosa adjacent to the scar in five and infiltrated into the submucosa in two. Most of these residual cancers were characterized by a lesion with a diameter exceeding 15 mm and by the location in the body or cardia of the stomach. Lymph node metastases were observed in one patient whose carcinoma invaded the deeper submucosal layer. Assessment of the depth of entire invasion from the endoscopically-resected specimen was correct for six of 11 patients.

Conclusion Gastric carcinomas to be resected by EMR should be smaller, especially if located in the body or cardia. Accurate diagnosis of the width and depth of invasion is indispensable before proceeding to EMR. Surgery may be the treatment of choice when there is submucosal invasion.

The incidence of early gastric cancer, designated as a lesion confined to the mucosa or submucosa, regardless of the presence or absence of lymph node metastasis, has increased steadily. The present rate is approximately 60 per cent of all resected cases of gastric cancer[1]. Recently, endoscopic mucosal resection (EMR) has been widely accepted for treatment of early gastric cancer because of the minimal invasiveness of the procedure and sustained quality of life. Current indications for EMR in patients with early gastric cancer are (1) type IIa well differentiated carcinoma less than 2 cm diameter and (2) type IIc well differentiated carcinoma without ulceration less than 1 cm in diameter[1]. Under certain conditions, endoscopic therapy can be curative; however, this is not the case in all patients.

Since 1990, EMR has been used for selected patients with early gastric cancer. The pathological findings were reviewed in patients who underwent subsequent gastric resection following EMR.

Patients and methods

Between January 1990 and August 1995, 39 patients with early gastric cancer were treated with EMR in Fukuoka City Hospital (*Table 1*). Eighty-five other patients with early gastric cancer had surgery during the same interval EMR was used when a lesion consisting of well or moderately differentiated adenocarcinoma had a diameter of less than 2 cm. Of these 39 patients, 11 underwent surgery following EMR. The time between EMR and subsequent operation ranged from 15 to 123 (mean 52) days. The reasons for subsequent surgical treatment are listed in *Table 2*. Patients with concomitant cancers of the sigmoid colon (one patient) and oesophagus (one patient) detected during follow-up underwent distal gastrectomy with sigmoid colectomy and proximal gastrectomy with oesophagectomy respectively One patient developed symptomatic gallstones and, although biopsy after EMR showed no evidence of malignancy, he had a distal gastrectomy with cholecystectomy.

Data on the 11 patients who had subsequent surgery were reviewed retrospectively. Endoscopically-resected specimens were examined by semiserial sections made every 2 mm.

Table 1 Early gastric cancers treated by endoscopic mucosal resection

	January 1990–May 1992	June 1992–December 1993	January 1994–August 1995	Total
Patients treated by endoscopic mucosal resection	15	12	12	39
Patients undergoing additional surgery	7	4	0	11

Table 2 Reasons for subsequent surgery

	No. of patients
Positive resection margin*	3
Submucosal invasion	5 (2)
Concomitant malignancy	
With positive resection margin	1
With submucosal invasion	1 (1)
Needed cholecystectomy	1

Values in parentheses indicate the number of patients with a lesion with lymphatic or vascular invasion *Cancer cells remained in the mucosa around the resection margin

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Histological examination of the entire cancerous lesion in the resected stomach was made using stepwise parallel sections 4 mm in thickness, each of which was stained with haematoxylin and eosin All specimens, including the resected stomach and regional lymph nodes, were reviewed Location and macroscopic classification were made according to the outlines prepared by the Japanese Gastroenterological Society[2]. Histological differentiation was grouped into three types, based on the outlines proposed by the Union Internacional Contra la Cancrum (UICC)[3]: well differentiated, moderately differentiated and poorly differentiated adenocarcinoma.

Twenty-eight of the patients who had EMR did not undergo additional surgery but had follow-up by endoscopy and biopsy. Eight developed local recurrence and required further EMR. Three died from unrelated causes but the remainder are alive with no evidence of recurrence at the time of writing.

Results

All 11 patients were men, of mean age 66 (range 50–81) years. Upper gastrointestinal radiographs and endoscopic photographs were available for these patients before EMR. Four carcinomas were located in the cardia of the stomach, four in the body and three in the antrum (*Table 3*). The largest diameter of the lesion was a mean 16 (range 11–20) mm. One patient had a depressed lesion (type IIc), while ten carcinomas were raised and were classified type IIa in eight patients, type IIa + IIc in one and type I in one. Biopsy showed that the adenocarcinoma was well differentiated in nine and moderately differentiated in two. None of the patients had an accompanying peptic ulcer.

Histology of the endoscopically-resected specimen

The safety margin and the maximum depth of invasion were confirmed microscopically in the endoscopically-resected specimen. Cancer invasion was examined both horizontally and vertically. Cancer cells remained in the mucosa around the resection margins in seven patients, there was infiltration of cancer cells in the submucosal layer in six, and lymphatic or vascular invasion was observed in three cases in which cancer cells had invaded the submucosa. EMR was repeated in two patients, in whom malignant cells were likely to remain in the mucosa around the resection margin. These two patients had subsequent surgery because of a positive resection margin in one and submucosal invasion in one patient. The remaining nine patients had surgery after primary EMR.

Histological findings after gastric resection

Malignant tissue in the gastric wall was completely removed in four patients, while cancer cells remained in the mucosa adjacent to the EMR scar in five and infiltrated into the submucosa in two patients (*Fig 1*). Six of the seven patients with residual tumour had an initial cancer with a diameter of at least 15 mm. Five of the residual tumours occurred in the body or cardia of the stomach. Lymph node metastasis, as well as lymphatic and vascular invasion, was observed in one patient, in whom cancer cells had invaded the deeper layer of the submucosa. In this patient, a raised lesion (type I) had been incompletely resected by EMR. Histologically, there was evidence of a shallow depressed lesion exceeding 2 cm in diameter adjacent to the scar, thereby indicating an early cancer classified as type I + IIc.

A comparison of the depth of invasion between endoscopically-resected and surgically-resected specimens is shown in *Table 4*. No cancer cells were found in four of 11 cases. Four of five residual tumours were confined to the mucosa in the endoscopically-resected specimen and had similar invasion in the surgically-resected specimen. In six patients with submucosal invasion in the endoscopically-resected specimen, the mucosa was invaded in one and the submucosa was invaded in two when the depth of invasion was assessed in the surgically-resected specimen. Hence, assessment of the depth of entire invasion from the endoscopically-resected specimens was correct in six of 11 cases.

Prognosis

Follow-up in these 11 patients ranged from 2 years and 11 months to 5 years and 9 months. Only one patient developed recurrent carcinoma. The original carcinoma invaded the submucosa and was accompanied by vascular invasion. There was no evidence of residual tumour in the resected stomach or lymph nodes; however, the patient died from multiple liver metastases 2 years and 8 months after EMR and subsequent proximal gastrectomy. In this

Table 3 Clinical data on 11 patients who had gastric resection after endoscopic mucosal resection for early gastric cancer

		Clinical findings before EMR				Endoscopically-resected specimen				Surgically-resected specimen			
Patient no.	Age (years)	Site of tumour	Size (mm)	Gross type	Histological type	Horizontal margin*	Depth of invasion	Lymphatic permeation	Vascular invasion	Residual cancer	Lymphatic permeation	Vascular invasion	Lymph node metastasis
1	55	A-Min	16	IIc	Well	–	m	–	–	–	–	–	–
2	72	M-Ant	18	IIa	Well	–	sm_2	+	–	–	–	–	–
3	56	M-Ant	14	IIa	Well	–	sm_2	+	+	–	–	–	–
4	67	C-Min	13	IIa	Moderately	+	sm_3	–	+	–	–	–	–
5	73	M-Maj	20	IIa	Well	+	m	–	–	m	–	–	–
6	78	M-Post	17	IIa	Well	+	m	–	–	m	–	–	–
7	60	A-Ant	20	IIa	Well	+	m	–	–	m	–	–	–
8†	71	C-Min	16	IIa	Well	+	m	–	–	m	–	–	–
9†	50	A-Maj	15	IIa + IIc	Well	–	sm_2	–	–	m	–	–	–
10	61	C-Post	11	IIa	Well	+	sm_2	–	–	sm_1	–	–	–
11	81	C-Post	20	I‡	Moderately	+	sm_2	–	–	sm_3	+	+	+

*Cancer cells remaining in the mucosa around the resection margin. †Patients who were treated with repeated endoscopic mucosal resection (EMR) ‡Histological examination of the resected stomach following EMR revealed a coexisting type IIc lesion adjacent to the type I lesion A, lower portion of the stomach; M, middle portion of the stomach, C, upper portion of the stomach, Ant, anterior wall; Post, posterior wall: Min, lesser curvature; Maj, greater curvature; Well, well differentiated adenocarcinoma; Moderately, moderately differentiated adenocarcinoma; m, mucosa; sm_1, superficial submucosal layer, sm_2, middle submucosal layer, sm_3, deeper submucosal layer

Table 3 Transpapillary cyst drainage

Reference	Year	No. of patients	Stent type (Fr)	Mean stent duration (months)	Site of stent tip	Initial NCD	Complications*	Initial success	Recurrences	Long-term success	Mean follow-up (months)
Smits *et al*[11]	1995	12	7/10 A	3	PC	Some	1 proximal stent migration 1 bleeding 1 infection	7	0	7	32
Barthet *et al*[12]	1995	20	7/10 P	4	n.s.	Some	1 acute pancreatitis 1 MPD stricture	18	2	16	15
Catalano *et al.*[26]	1995	21	5/10 P	2	PC 13 BS 8	No	1 acute pancreatitis	17	1	16	37
Binmoeller *et al.*[13]	1995	33	5/7	n.s.	PC	No	1 acute pancreatitis 2 pseudocyst infection	31	5	26	22
Dohmoto and Rupp[20]	1994	13	5/7	6	BS	No		9	1	8	n.s.
Kozarek *et al*[18]	1985	18	5/7 A	2	BS	Some	2 acute pancreatitis 2 stent blockages + acute pancreatitis 1 MPD stricture	16	1	15	16
Total		117	—	—	—	—	—	98 (84)	10 (9)	88 (75)	15–37

Values in parentheses are percentages *No complication required surgery. NCD, nasocystic drain; A, Amsterdam; P, pigtail; PC, in pseudocyst; BS, beyond pseudocyst or stricture (within the main pancreatic duct (MPD)); n.s., not stated

Table 4 Combined procedures and other series

Reference	Year	No. of patients	Procedure type	Technical failures	Bleeding*	Other complications*	Initial success	Recurrences	Long-term success	Mean follow-up (months)
Smits *et al*[11]	1995	8	4 ECG/TCD 2 ECD/TCD 1 ECG/ECD 1 ECG/ECD/TCD	0	0	0	8	1	7	32
Barthet *et al.*[12]	1995	10	5 ECG/TCD 5 ECD/TCD	0	0	1 (0) pancreatic ascites	10	3	7	15
Dohmoto and Rupp[20]	1994	3	3 ECG/TCD	0	1 (1) ECG	0	2	1	1	n s
Binmoeller *et al*[13]	1995	24	4 ECG or ECD/TCD 20 ECD or ECG	1	1(1) ECD 1 (1) ECG	1 (1) gallbladder perforation	20	6	14	22

Values in parentheses are percentages or *complications requiring surgery. ECG, endoscopic cystogastrostomy; TCD, transpapillary cystic drainage; ECD, endoscopic cystoduodenostomy; n.s., not stated

of the recurrences were successfully drained by repeat TCD; the remainder were treated conservatively or by open surgery.

The position of the tip of the pancreatic stent is controversial. Barthet *et al.*[12] favour insertion of the stent tip into the pseudocyst cavity. In their series complete resolution occurred in 11 of 12 patients when the stent was in the cyst, compared with 12 of 18 when the stent tip lay in the pancreatic duct because it could not be advanced into the cyst cavity. Catalano *et al.*[26] found no difference in success with the position of the catheter tip provided it was distal to any stricture within the main pancreatic duct. Dohmoto and Rupp[20] also stressed the importance of stent placement beyond the pseudocyst connection to allow free drainage. Overall, there is scant evidence that placement of the stent tip into the pseudocyst cavity confers any advantage. The site of the pseudocyst itself may be important. Barthet *et al.*[12] and Catalano and colleagues[26] both had more failures with pseudocysts in the pancreatic tail, despite technical success of stent placement.

Procedure-related complications are few and there have been no deaths associated with TCD. Of the 117 patients described in *Table 3* there was a single case of bleeding which did not require intervention[11]; six patients developed pancreatitis, in all cases mild and self-limiting. Stent blockage was uncommon, presumably because of the short duration of placement. One patient had migration of the stent proximally into the main duct which could not be retrieved subsequently. However, there have been no clinical sequelae as a result at 29 months' follow-up[11]. There were three cases of secondary pseudocyst infection all of which resolved with stent change[11,13]. Barthet *et al.*[12] compared the outcome of TCD alone and TCD combined with a transmural drainage procedure. Ten patients had combined transmural and transpapillary drainage and no advantage was found compared with the 20 patients who had no visible bulge in the gastro-

Table 1 Endoscopic cystgastrostomy

Reference	Year	No of patients	ECG size (mm)	Stent type (Fr)	NCD	Technical failures	Bleeding*	Other complications*	Initial success	Recurrences	Long-term success	Follow-up (months)
Smits *et al.*[11]	1995	10	3–5	7/10 A	No	3	2 (1)	2 (0) perforations	6	3	3	32
Cremer *et al*[19]	1989	11	10	No	All	0	1 (1)	2 (0) infections	11	2	9	18
Dohmoto and Rupp[20]	1994	10	5	7 P	No	0	—	—	10	2	8	n.s.
Howell *et al.*[21]	1993	4	20–50	10 P	Most	0	1 (1)	—	3	0	3	48
Funnell *et al.*[22]	1994	2	10	10 A	1	0	—	—	2	0	2	9
Bejanin *et al.*[23]	1993	13	n.s.	n.s.	n.s.	2	0	2 (2) perforations 1 (0) infection	9	2	7	33
Total		50	—	—	—	5	4 (3)	4 (2) perforations 3 (0) infections	41 (82)	9 (18)	32 (64)	9–48

Values in parentheses are percentages or *complications requiring surgery. ECG, endoscopic cystogastrostomy; NCD, nasocystic drain; A, Amsterdam; P, pigtail; n.s., not stated

Table 2 Endoscopic cystoduodenostomy

Reference	Year	No. of patients	ECD size (mm)	Stent type (Fr)	NCD	Technical failures	Bleeding*	Other complications*	Initial success	Recurrences	Long-term success	Follow-up (months)
Smits *et al.*[11]	1995	7	3–5	7/10 A	No	0	0	0	7	0	7	32
Sahel *et al.*[24]	1987	19	10–15	No	Some	2	2 (1†)	1 (0) cholecystitis 2 (0) perforations	15	0	15	20
Cremer *et al.*[19]	1989	22	8	No	All	1	0	1 (0) perforation	21	2	19	35
Dohmoto and Rupp[20]	1994	3	5	7 P	1	0	0	0	3	0	3	n.s.
Howell *et al.*[21]	1993	4	20–50	10 P	Most	0	0	0	4	0	4	48
Funnell *et al.*[22]	1994	3	10	10 A	1	0	0	0	3	0	3	9
Bejanin *et al.*[23]	1993	13	n.s.	n s.	No	2	1 (1)	0	10	2	8	33
Total		71	—	—	—	5	3 (2)	4 (0)	63 (89)	4 (6)	59 (83)	9–48

Values in parentheses are percentages or *complications requiring emergency surgery. †Patient died. ECD, endoscopic cystoduodenostomy; NCD, nasocystic drain; A, Amsterdam; P, pigtail; n.s., not stated

The first transpapillary drainage was reported in 1984 by Hershfield[25] who successfully aspirated a large pseudocyst via the accessory pancreatic duct without recurrence. Since then, there have been a number of case reports and six studies that have included ten or more patients (*Table 3*). In addition there are several series of patients in which TCD and transmural drainage have been performed in the same patient[11–13,20] or where a distinction between ECD and ECG has not been made[13]. The results of these studies are shown in *Table 4*.

Transpapillary cyst drainage

TCD is possible in pseudocysts where there is communication between the pancreatic ductal system and the pseudocyst, often with an associated proximal ductal obstruction by stones or stricture[12]. Communication between pseudocysts and ducts occurs in 40–69 per cent of pseudocysts as a whole[27–29] and is commoner in pseudocysts associated with chronic rather than with acute pancreatitis (20 per cent in acute pancreatitis *versus* 49 per cent in chronic pancreatitis[12]). It is hypothesized that these pseudocysts develop from ductal distension proximal to the stricture causing rupture of the smaller ducts and pseudocyst formation[20].

The technique of TCD is technically demanding[2,30]. At endoscopic retrograde cholangiopancreatography (ERCP) a 0·9-mm (0·035 inch) guidewire is advanced along the main pancreatic duct beyond the pseudocyst or manipulated via the main duct into the pseudocyst cavity. A pancreatic duct sphincterotomy is performed in most patients and a 5- or 7-Fr stent is placed and left *in situ* for a mean period of 3 months. Some authors have also routinely placed a nasocystic drain, allowing pus or debris to be flushed out. Antibiotic prophylaxis is given before all procedures.

In the combined series of 117 patients (*Table 3*) successful drainage was achieved in 84 per cent with a 9 per cent recurrence rate over a mean follow-up of 2 years. Three

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Review

Endoscopic management of pancreatic pseudocysts

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Background Pancreatic pseudocysts may produce pain, or biliary or duodenal obstruction. Those over 6 cm in diameter or associated with chronic pancreatitis are unlikely to resolve and usually require intervention. There are a number of treatment modalities available and this paper reviews the role of endoscopic drainage.

Methods All articles and case reports quoted on Medline (National Library of Medicine, Washington DC, USA) containing the text words 'endoscopy' and 'pseudocyst', and citations from these references were reviewed.

Results Endoscopic drainage is technically feasible in around 50 per cent of pancreatic pseudocysts associated with chronic pancreatitis. Successful drainage occurred in 82–89 per cent. The major complication is bleeding which required surgery for control in 5 per cent of procedures. One death attributable to the procedure has been reported. Recurrence rates range from 6 to 18 per cent with up to 4 years' follow-up. As in open surgery, recurrence is highest with drainage via the stomach.

Conclusion Endoscopic drainage provides a minimally invasive approach to pseudocyst management, with success and recurrence rates similar to those of open surgery but with lower morbidity and mortality rates. It should be considered the treatment of choice for pseudocysts less than 1 cm thick which bulge into the stomach or duodenum, or for those which communicate with the main pancreatic duct.

Pancreatic pseudocysts are fluid collections arising in or adjacent to the pancreas but lacking an epithelial lining[1]. Pseudocysts are usually rich in pancreatic secretions, which have leaked from a duct system disrupted by acute inflammation, trauma or obstruction by stricture or stone[2]. The majority of peripancreatic fluid collections associated with acute pancreatitis resolve spontaneously and seldom require intervention[3–5]. In contrast, pseudocysts associated with chronic pancreatitis usually have a mature capsule and infrequently regress if over 6 cm in diameter[6,7]. Pseudocysts of this size occur in around 25 per cent of patients with chronic pancreatitis at some time in the course of the disease[8,9]. Less than 10 per cent resolve spontaneously[3,10] and their management has become more complex with an increasing number of treatment options available, including percutaneous aspiration, percutaneous drainage, surgery and, more recently, endoscopic drainage.

Descriptions of endoscopic drainage techniques have been largely in the form of case reports or small series combining the results of transpapillary cyst drainage (TCD) and transmural techniques (endoscopic cystgastrostomy (ECG) and endoscopic cystduodenostomy (ECD)) making evaluation of the complications and outcome of each technique difficult. In the past 2 years, however, there have been a number of papers reporting larger series of 20–30 patients allowing an improved assessment of the role of these techniques in the management of pseudocysts[11–13]. This paper provides a critical review of the technical success, complications and recurrence rate associated with endoscopic drainage.

History

The first reported attempt at endoscopic pseudocyst drainage was in 1975[14]. Using a 21-G needle the authors aspirated 60 ml through the posterior wall of the stomach. There was no symptomatic relief and no further endoscopic intervention was performed. In 1982 Aranha *et al.*[15] attempted ECG on two patients who were medically unfit for surgery. Endoscopic diathermy was used to create a hole through the posterior wall of the stomach; 400 ml drained successfully from one patient who died the following day from myocardial infarction and the second procedure was abandoned because of excessive bleeding. The first successfully completed transmural drainage procedures were described at the 1983 American Society of Gastroenterology meeting as a case report by Khawaja and Goldman[16], and in four patients by Kozarek *et al.*[17] subsequently reported in more detail elsewhere[18]. Kozarek and colleagues used a side-viewing endoscope and a modified straight wire sphincterotome to perform three ECGs and one ECD. This achieved successful drainage in three patients, although one died from a variceal bleed and liver failure a few days after the procedure

These early results with low success rates (three of eight successful) and high mortality rate (two of eight) led to disregard of the technique by several authors[1,15]. The high perioperative mortality rate associated with these initial procedures was in part attributable to their restricted use in patients deemed unfit for surgery because of co-morbid conditions and previous failed surgical procedures. Technical advances, increasing operator experience and refinement of the indications have now led to a resurgence in popularity of the technique. *Tables 1* and *2* show the collected results of studies with more than eight patients. Resolution of the pseudocyst has been used as the main outcome measure.

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- Scheduled review date
- Linked to audit

Guidelines may be used to support individual decisions or a set of guidelines may be prepared which covers a whole episode of care, for example to cover the 2 days immediately following cardiac surgery. These sets of guidelines are called critical pathways[3] and are increasingly used, not always to the satisfaction of clinicians, in 'managed care'.

Clinicians have worried that the development of guidelines will increase the risk of litigation but evidence from the USA does not support this fear[4]; the existence of guidelines may be used to support the clinician's actions or may dissuade a lawyer from proceeding with litigation. In the UK the Bolam test is the key criterion and this test is to compare the clinical behaviour in question with standard or usual care. If the guideline reflects usual care the clinician could be liable; if the guideline contains the latest research which is as yet not generally implemented, the guideline could not be used as evidence of the required standard of care[1].

Guidelines should be helpful and not threatening, and they should be owned and developed by the medical profession, based on the best evidence and with patients involved. If the profession is dilatory in guideline development there is a risk that guidelines may be developed for them.

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Evidence-based, locally owned, patient-centred guideline development

Research gets into practice by two main routes. One is by the incorporation of evidence in an individual clinical decision; the other is the incorporation of evidence into clinical policies and systems of care to ensure that those policies are put into practice.

- A policy is a statement of what *should* be done.
- A system is an integrated set of activities which *ensure* that the policy will be put into practice.
- Guidelines set out *how the objective will be achieved.* They have been defined as 'systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances'[1]. There are three types of guidelines: diagnostic, referral and discharge, and treatment and self-care.
- Audit or utilization review measures *how well* a system is performing.

Quality assurance systems *improve the performance* of the system and the professionals who work within it with respect to explicit standards.

Two types of guidelines have been produced in the past: national guidelines and local guidelines. National guidelines often have a very sound evidence base. Unfortunately they may have limited impact because people are suspicious about guidelines written by those whom they do not know and which do not appear to take into account their particular circumstances. Locally produced guidelines, on the other hand, can be very influential because they involve that most important ingredient, the potential users of the guidelines. However, locally produced guidelines may at best duplicate the searching and appraising of evidence, and at worst may not be based on best current evidence.

There is a tale, for which one has no good evidence but it is a good tale, that Mary Baker, who invented the first instant cake mix, was worried by the fact that her powdered cake mix was not selling. Someone suggested that she take out the powdered egg and let the person making the cake break in their own real raw egg. She did this and the rest, as they say, is history. The same seems to hold true for the development of guidelines, namely that local involvement is essential if they are to be influential. Guidelines may therefore be used not simply as a distillate of knowledge but also as a means of expressing and developing local clinical consensus. There is evidence that guidelines given without any human contact are ineffective[2]. The best approach, therefore, is to develop a good evidence base that can be used in guideline development and allow local groups to build on the evidence, taking into account local circumstances.

Patients are being involved increasingly in guideline development, not only to improve readability but also to ensure that the topics covered are those which are of interest to patients and not simply those for which there is good research-based knowledge. The final formula, therefore, for an evidence-based effective guideline may be expressed simply thus:

Best current knowledge (needs to be done only once)	+	local involvement of potential users	+	patient involvement	=	evidence-based effective guidelines

A useful checklist of desirable attributes for appraising guidelines is set out below.

- Validity
- Cost-effectiveness
- Reproducibility
- Reliability
- Patient and user involvement
- Clinical applicability
- Clinical flexibility
- Clarity
- Meticulous documentation

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and patients with two or more genetic defects should be given preventive therapy liberally. Lifelong anticoagulation should be recommended for patients with a factor V Leiden mutation and two or more thrombotic episodes[11].

Special attention is required when thrombosis occurs at an unusual location or when the first manifestation is at a young or advanced age. Apart from secondary causes of thrombosis, the presence of a primary hypercoagulation disorder should also be ruled out, testing especially for the commonest, APC resistance. Recently, the authors were confronted with a 63-year-old patient with mesenteric ischaemia in whom intraoperative findings and histology confirmed mesenteric vein thrombosis. Routine coagulation studies, including fibrinogen level, platelet count, partial thromboplastin time and prothrombin time were normal, as were tests measuring factor deficiencies of the clotting system (antithrombin III, protein C/S, factor V and VIII). Doubting an idiopathic cause the newly developed test for APC resistance was performed to identify any possible APC-induced prolongation of the activated partial thromboplastin time: the test proved positive. The patient was treated by segmental small bowel resection and anticoagulation with coumadin with a satisfactory outcome. To the authors' knowledge, this is the first reported case of the APC resistance disorder appearing as venous thrombosis at an atypical site at an advanced age.

At this time the following guidelines seem appropriate. Investigation for the hypercoagulation disorder APC resistance should be initiated in the following circumstances.

1 In all patients with venous thrombosis at a young or advanced age, especially when there are no predisposing risk factors.
2 In patients with or without venous thrombosis who have a positive family history of thrombosis.
3 In patients with thrombosis at an unusual location (e.g. gastrointestinal tract).
4 In offspring of patients with APC resistance to assess autosomal dominant trait inheritance, to institute prophylactic treatment and to prevent medication with thrombogenic drugs (e.g. contraceptives).

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British Journal of Surgery 1997, 84, 1633–1635

Leading articles

Activated protein C resistance: the commonest hereditary hypercoagulation disorder

Venous thrombosis remains a life-threatening event with a current annual incidence of 1 in 1000; it is responsible for an estimated 100000 deaths each year in Germany[1]. The pathogenesis is mainly attributed to disturbances of blood flow, vessel surface and/or blood constituents. The vast majority of venous thromboses occur in the deep veins of the legs and pelvis, with consecutive pulmonary embolism, or involve the cerebral vessels[2]. Venous thrombosis may be of genetic and/or acquired aetiology. Differentiation between primary and secondary causes is essential, not only for treatment of the patient but also the patient's offspring.

Most hereditary coagulation defects become evident before 45 years of age and are associated with a family history of thrombosis, indicating the involvement of genetic factors. Until fairly recently defects in the four major coagulation pathways (antithrombin, protein C/protein S, the fibrinolytic system and tissue factor inhibitors) were considered chiefly responsible, yet they accounted for only about 15 per cent of cases of inherited thrombophilia and for less than 5 per cent of all venous thromboses; a substantial number of patients remained undiagnosed[3]. It was not until 1994 that the majority of patients with inherited hypercoagulation disorders could be categorized. The commonest inherited pathogenetic risk factor for venous thrombosis is now known to be resistance to activated protein C (APC) or factor V Leiden (so named after the location of its discovery). APC is a vitamin K-dependent anticoagulant serine protease which, in the anticoagulant protein C pathway, functions as an inactivator of factor Va and VIIIa[4,5]. A poor response or resistance to APC leads to thrombophilia. On a molecular basis this disorder is associated with a single point mutation of the factor V gene in over 97 per cent of cases. Replacement of arginine by glutamine at the APC cleavage site results in a selective loss of the anticoagulant activity of factor V or an increased resistance to APC of the mutant factor Va itself[6,7].

APC resistance in a consecutive series of patients with venous thrombosis was positive in 40–60 per cent, making it commoner than all other genetic hypercoagulation predispositions combined[8]. In the same study a surprisingly high prevalence of 3–7 per cent was detected in the healthy control group. This genetic coagulation defect reaches particularly high frequencies in Europe, with carrier rates of 15 per cent in Greeks, 8·8 per cent in UK whites and 6 per cent in men of European origin in North America. Outside Europe, the mutation is rare, with an allele frequency of 0·6 per cent in Asia Minor; it does not occur in the indigenous populations of south-east Asia, Africa, America or Australasia[9].

APC resistance presents as an autosomal dominant trait with a heterozygous or homozygous pattern. Because of the high allele frequency of the mutated factor V gene, homozygous carriers are not as rare as in other types of hereditary thrombophilia. Heterozygous APC resistance inflicts a lifelong risk of thrombosis but, unless associated with other genetic defects or situations provoking thrombosis, thrombotic events may not present until an advanced age. Heterozygotes have between a fivefold and tenfold and homozygotes a 50- to 100-fold increased risk of venous thrombosis. An important group at risk are women with APC resistance taking contraceptive drugs; heterozygotes are 30 times and homozygotes as much as 200 times more susceptible to thrombosis than the normal population[10].

The treatment of individuals who are heterozygous for the factor V mutation but have no personal or family history of thrombosis or other anticoagulant defects should consist of prophylactic anticoagulant therapy in situations prone to cause thrombosis (e.g. major surgery, immobilization). Counselling about the risk of thrombosis and avoidance of oral contraceptives should be recommended. In heterozygote patients with a history of thrombosis the same treatment as for deficiencies of protein C/S or antithrombin III should be instituted. Homozygotes

Typescripts

Manuscripts must be clearly reproduced with adequate space for editorial notes. **Type or print the text on one side of sheets of A4 paper (210 × 297 mm) with double spacing and 4-cm margins. Manuscripts that do not conform to these requirements will be returned to you for recasting.** Begin each section (abstract, introduction, patients and methods, results, and discussion) on a new page.

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On the title page give: (1) the title of the article, (2) the name and initials of each author; (3) the department and institution to which the work should be attributed; (4) the name, address, and telephone, facsimile and e-mail numbers of the author responsible for correspondence and to whom requests for reprints should be addressed; (5) sources of financial support, and (6) the category in which the manuscript is being submitted (original article, review etc.).

Abstract

This should be not more than 200 words on the second page of the manuscript and be presented in a structured format. **Background:** state why the study was done, and its main aim, **Method:** describe patients, laboratory material and other methods used. Clearly identify the nature of the study: randomized controlled trial, retrospective review, experimental study, etc **Results:** state the main findings of the study; include important numerical values **Conclusion:** state the main conclusion drawn from the results. Controversial or unexpected observations may be highlighted, but keep this section brief. Write the abstract in clear prose

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Abbreviations

Use abbreviations sparingly. Terms that are mentioned frequently may be abbreviated but only if this does not impair comprehension by the reader. Use abbreviations consistently throughout the text and clearly define each one on first use.

Numbers and units

Use the decimal point, not a comma, e.g. 5 7. Use a space and not a comma after thousands and multiples thereof, e.g. 10 000. Use SI units (International System of Units) except for the measurement of blood pressure (mmHg) Where measurements were made in non-SI units, give the actual values and units, with SI equivalents inserted in parentheses at appropriate points.

Statistics

For detailed guidance on the handling of statistical material, consult *Br J Surg* 1991, 78 782–4. In evaluating a manuscript the Editors and statistical referees will consider the design of the study, the presentation and analysis of data and the interpretation of results.

Design

Set out clearly the objectives of the study, identify the primary and secondary hypotheses, and the chosen end-points, and explain the rationale for the choice of sample size. Investigators embarking on randomized controlled studies may wish to consider the CONSORT statement (*JAMA* 1996, **276**. 637–9)

Presentation

Whenever possible use graphical presentation to illustrate the main findings of a study. The use of standard deviation and standard error should be clearly distinguished. Do not use the '±' symbol; these statistics should be presented in parentheses after the mean value

Analysis

Clearly describe which methods were used for which analyses; any methods not in common usage should be supported by references. Report results of statistical tests by stating the value of the test statistic, the number of degrees of freedom and the *P* value, e.g. '$t = 1{\cdot}34$, 16 d.f., $P = 0{\cdot}20$'.

Actual *P* values should be reported to two decimal places, especially when the result is not significant, rather than stating 'not significant'. Whenever possible, the results of the primary analyses should be reported using confidence intervals instead of, or in addition to, *P* values

Interpretation

Do not confuse statistical significance with clinical significance. In particular, 'negative' findings should be interpreted through the use of confidence intervals.

Beware of placing undue emphasis on secondary analyses, especially when they are suggested by an inspection of the data.

References

Type the references with double spacing in the Vancouver style (see above· Uniform Requirements for Manuscripts Submitted to Biomedical Journals). Reference to abstracts from meetings is discouraged Reference to unpublished communications will not be accepted. Cite personal communications in the text, in parentheses. The first author is responsible for confirming the acceptability of the material quoted with the originator.

In the text, number the references consecutively by superscript: ^{1} or $^{1-3}$. References cited only in tables or figures should be numbered in sequence according to the first mention of the table or figure in the text. The sequence for a standard journal article should be author(s), title of paper; journal name abbreviated as in Index Medicus (written in full if no abbreviation is quoted); year of publication; volume number; page numbers. For example. De Bolla AR, Obeid ML. Mortality in acute pancreatitis. *Ann R Coll Surg Engl* 1984; 66: 184–6. The sequence for the chapters of a book should be author(s); chapter title; editors; book title; place of publication, publisher, year of publication; page numbers. For example: Calenoff L, Rogers L. Esophageal complications of surgery and lifesaving procedures In: Meyers M, Ghahremani G, eds. *Iatrogenic Gastrointestinal Complications* New York: Springer, 1981: 123–63

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The Editorial Board of *The British Journal of Surgery* encourages submission of review articles on topics of interest to its readers. Any topic will be considered, but priority will be given to those addressing a major current problem. The author of each accepted review will receive an honorarium. Potential authors seeking advice on the suitability of review topics are advised to contact: Mr J. A. Murie, University Department of Surgery, The Royal Infirmary, Edinburgh EH3 9YW, UK.

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Notices and announcements

6–19 November 1997
Hong Kong International Cancer Conference and Asian Pacific Cancer Congress 1997
Hong Kong
Information. Department of Surgery, The University of Hong Kong, Queen Mary Hospital, Hong Kong

9–14 November 1997
Health Technology Assessment: the Pathway to Evidence-Based Practice – the UK Experience
Manchester, UK
Information Promotions Manager, International Seminars, The British Council, 1 Beaumont Place, Oxford OX1 2PJ, UK

27–28 November 1997
31st Meeting of the Vascular Surgical Society of Great Britain and Ireland
London, UK
Information T. Szymanska, Vascular Surgical Society of Great Britain and Ireland, Countess of Chester Hospital, Liverpool Road, Chester CH2 1BQ, UK

25 February–1 March 1998
IX Asean Congress of Plastic Surgery
Penang, Malaysia
Information. M. Subramaniam, Department of Plastic Surgery, Hospital Ipoh, 30990 Ipoh, Perak, Malaysia

26–27 March 1998
3rd M62 Coloproctology Course
Manchester, UK
Information J. Hill, Department of General and Colorectal Surgery, Central Manchester Healthcare Trust, Oxford Road, Manchester M13 9WL, UK

20–22 April 1998
The Paediatric Oesophagus. An Interdisciplinary Symposium. Main Topic: Gastro-Oesophageal Reflux with a Special Interest in Alkaline Reflux
Izmir, Turkey
Information. O Mutaf, Department of Paediatric Surgery, Ege University Faculty of Medicine, 35100 Izmir, Turkey

13–15 May 1998
Association of Surgeons of Great Britain and Ireland
Edinburgh, UK
Information. Association of Surgeons of Great Britain and Ireland, The Royal College of Surgeons of England, 35–43 Lincoln's Inn Fields, London WC2A 3PN, UK

20–24 June 1998
Therapeutic Options for the Locally Advanced Non-Small Cell Lung Cancer
Terme di Valdieri, Italy
Information· G. Buccheri, Scientific Secretary, Ospedale A Carle, 1-12100 Roccavione (CN), Italy

12–17 July 1998
XVII World Congress of the Transplantation Society
Montréal, Canada
Information. L. Felicissimo and Associates, 12449 rue Cousineau, Montréal, Québec, Canada H4K 1P9

particularly those experiencing a short period of plastic surgery training, I believe it has considerable potential as an easy sort of reference in many plastic surgery wards, especially by nursing staff.

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Rectal Cancer Surgery. Optimisation – Standardisation – Documentation

O. Søreide and J. Norstein (eds). 240 × 160 mm. Pp. 457. Illustrated. 1997. Berlin: Springer. DM 178,00.

I had great expectations of reading this book and a feeling that I might have covered the entire range of rectal cancer surgery; despite a list of 56 contributors from all over the world and 31 chapters, I was disappointed. There is quite sufficient information to give even the most avid rectal cancer surgeon a good read, but the way in which the volume has been put together detracts from its appeal. At least nine chapters only reiterate previous chapters and there are a large number of common references between these chapters, making the book a little difficult to read. Still, if one picks out certain aspects of colorectal cancer on which to concentrate in respect of surgical treatment, the book is no doubt able to give some of the answers. I was a little disappointed that in the section on surgical technique the option of a resection and a stoma had not been appraised Although the ideal is to allow all patients the opportunity of a restorative resection there is still a place for the non-restorative procedure. In general, the chapters are well referenced and well written. However, reading the individual contributions I felt that the authors had not been given the opportunity to see the text of their fellow authors and so the book lost some of its interest. The most interesting and certainly most thought-provoking chapter was the last, which discussed the question of international standardization and documentation of the treatment of rectal cancer; this should provoke anybody involved in the treatment of rectal cancer radiologically, chemotherapeutically or surgically to think very carefully about how he or she organizes practice and treatment.

The most important message that I took away from this book was that we should no longer feel able to deal with all patients with rectal cancer in an isolated practice and that we need the benefit of all specialists who have contributed to this book to enable us to offer an appropriate standard of care Despite its shortcomings, I think that anyone who has an interest in diseases of the colon and rectum should have at least a passing interest in reading this volume, although maybe not from cover to cover as I did.

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British Journal of Surgery 1997, 84, 1628–1629

Book reviews

Operative Otolaryngology Head and Neck Surgery (two volumes)

E. N. Myers (ed.). 285 × 220 mm. Pp. 1559. Illustrated. 1997. Philadelphia, Pennsylvania: W. B. Saunders. £250.

This is a form of surgical cook book. The senior editor, Eugene N. Myers, Professor and Chairman of the Department of Otolaryngology, together with eight subeditors from Pittsburgh School of Medicine have produced a weighty two-volume publication. The layout and quality of the figures and print is good. The book is divided broadly into 18 sections by anatomical area and occasionally by topic, such as vertigo and cranial base surgery. Each chapter is organized into a section covering the indications for surgery followed by a detailed decription of the surgical technique, postoperative management and complications. This book, as its title implies, is very much a book of ENT procedures, with approximately one-third of the 1559 pages dedicated to head and neck cancer. If there is a criticism, it is that the authors have tried to press too many topics into this publication and, as a result, the full range of surgical procedures is not discussed; only the tried and tested techniques are described. It is primarily about surgical procedures and has no pretension to be a major reference book. The advice and techniques recommended are sound. Eugene Myers writes with the natural authority of a senior surgeon.

This volume will be of interest primarily to surgeons training in otolaryngology and head and neck surgery, but it is also a useful book for surgeons who, by necessity, are faced with undertaking unfamiliar procedures in the head and neck. It gives good solid practical advice. I am pleased to have it in the department library.

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Progress in Surgery Volume 23. Gastroesophageal Reflux Disease (GERD): Back to Surgery?

M. W. Buchler, E. Frei, Ch. Klaiber and L. Krähenbuhl (eds). 245 × 175 mm. Pp. 248. Illustrated. 1997. Basel: Karger. Price not supplied.

At first sight this book looks too expensive, boringly repetitive and oddly structured. This is largely because it is the product of a symposium. But look closely, there are gems here. Gastro-oesophageal reflux, an apparently mundane subject, is changing rapidly. The principal manifestations of the change are the enormous increase in cancers of the lower oesophagus and cardia, and the advent of minimal access surgery for reflux control. To my mind, the best parts of this book are those that deal with epidemiology, the nature of the disease and the techniques of antireflux surgery. Many of the chapters are very well referenced. Newcomers and experienced surgeons alike will find much of interest. On the downside, several chapters are repetitive and of the 'this is how we do it here' variety. It is also inevitable that all books are somewhat out of date by the time they are printed, such is the pace of change. I would have liked to see more on methods of treating Barrett's oesophagus and some of the exciting experimental forms of treatment for reflux.

This is a volume for the oesophageal enthusiast. Rush out and buy a copy or, better still, get someone to buy one for you

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Surgery for Acquired Aortic Valve Disease

A. Piwnica and S. Westaby (eds). 280 × 192 mm. Pp. 485. Illustrated. 1996. Oxford: Isis Medical Media. £120.

This multiauthor text, written by an impressive array of international experts, covers the field of surgery for acquired aortic valve disease in a comprehensive manner. It is well presented with copious colour illustrations and I certainly enjoyed reading it. It provides an up-to-date view of surgery in this area and covers the technical aspects of the more complex operations. In fact it also considers some aspects of congenital aortic valve disease despite its title. This is an area of cardiac surgery which is changing with the resurgence of interest in homografts, the development of stentless valves and the pulmonary autograft operation. It therefore seems timely that an up-to-date overview of the subject should be presented. My only criticisms relate to the chapters on specific heart valves, which are basically written by proponents of the individual devices leading to obvious bias; this section takes on more the appearance of an industrial manual. I would prefer to have seen a much shorter section with a neutral overview of the performance of the replacement devices available. It would, I believe, be a worthwhile read for any cardiothoracic surgical trainee or established cardiac surgeon, although whether it offers more overall than some of the more comprehensive cardiac texts in this area is debatable.

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Fundamentals of Plastic Surgery

M. W. Marks and C. Marks. 261 × 187 mm. Pp. 400. Illustrated. 1997. Philadelphia, Pennsylvania: W. B. Saunders. £54.

The specialty of plastic surgery covers a wide spectrum and it is therefore difficult to provide a concise, up-to-date account of the full range. This book by two authors has, I feel, managed to achieve this aim.The spectrum of chapters ranges from craniofacial surgery through to aesthetic surgery, but includes basic knowledge on wound care. The written descriptions are kept short and are complemented by excellent illustrations and photographs. The microsurgery chapter, for instance, includes the full range of currently used free flaps, including vascularized bone grafts such as fibula, deep circumflex iliac artery and scapular flaps. Because it is an American production there are inevitably some differences from British treatment. With regard to other books in the market, the alternatives are limited. Perhaps the most straightforward and comprehensive at this level was the *ABC of Plastic & Reconstructive Surgery* by Dai Davis based on articles in the *British Medical Journal* published in 1985. This book, however, is really the next plane up in explanation and complexity. Although directed mainly at junior medical staff, Mr Leung *et al* reported a shorter average operating time in their series. In our series eight of 30 patients suffered acute cholecystitis and this may explain longer operating times.

Our patients experienced less postoperative pain. The presence of only one small plaster on the periumbilical wound and the injection of local anaesthetic may play a significant role in reducing the pain

In conclusion, acquired experience and typical Italian fantasy might explain the attempt to find new solutions. We are nevertheless conscious that this attitude remains useful only if a new procedure is not too challenging. Far from considering this technique as a procedure of choice we reported it as a different possibility that a laparoscopic surgeon might care to consider. We published this technique to expose our ideas to the opinion of others.

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Letter 3

Sir

There has been a recent trend towards performing laparoscopic cholecystectomy with fewer trocar wounds[1,2]. Dr Navarra *et al.* were one of the first to achieve one wound, even though the single incision is formed by joining the camera and adjacent 10-mm working ports.

Any new techniques should be subjected to the stringent process of objective evaluation by carefully balancing advantages against disadvantages: technical feasibility is not equivalent to validity of application. Second, the safety of the patient must always remain paramount. The liver hilum is no testing ground for the limits of laparoscopic surgical skills[3].

The first apparent advantage of the one-wound technique is the absence of subcostal and epigastric wounds but the single supraumbilical incision formed by cutting the tissue bridge (at least 1 cm in length to allow for some degree of movement between the bulky 10-mm sheaths) between the two 10-mm port wounds is just as long as the added length of the four-port wounds. There is no reason why postoperative pain should be less and hospital stay shorter. The requirement for postoperative analgesia has been shown to be unaffected[2,3] by the elimination of one- or two-port wounds. Besides, the healed 5-mm wounds in the classical technique are rather inconspicuous. The only advantage of Dr Navarra's approach is the easy extraction of an unusually large and hard stone through the conjoint wound.

Our experience with the one-wound technique has revealed many disadvantages. The umbilical working port is in a suboptimal position with the fulcrum too far away from the operative field With the instruments limited to the cephalad direction pointing towards the liver hilum, dissection of Calot's triangle is cumbersome and the use of clip-applier hazardous; the telescope and other instruments can become entangled. Traction using three sutures passed through the gallbladder wall is not ideal and leakage of potentially infected bile into the peritoneum or between layers of the gallbladder wall is undesirable and hinders clear dissection In the reverse Trendelenburg position with the liver sagging downwards, Calot's triangle cannot be satisfactorily 'opened up' using three subcostal traction sutures picking up the infundibulum and the adjacent areas (*Fig 1* of the original article). By contrast, in the standard four-port technique, Calot's triangle is satisfactorily displayed by drawing the infundibulum downwards and laterally with one grasping forceps while the dome of the gallbladder along with liver edge is retracted cephalad using another grasper underneath the thoracic cage. Increased technical difficulties were reflected by doubling of the operating time (a reported mean of 123 min). The risks of bile duct injury are increased. The absence of bile duct complications in the cohort of 30 patients is no proof of safety, given the fact that bile duct injury rates are calculated in terms of one patient in several hundreds. On balance, the minimal advantages of the described limited access technique are more than negated by its many disadvantages.

There is a hidden danger of wide publicity of the 'improved' approaches featuring fewer wounds Unprepared surgeons may yield to patient or family pressure to do a laparoscopic cholecystectomy using fewer ports under suboptimal conditions. In the current litigious climate, surgical misadventure from abandoning the safest, standard approach may prove too high a price to pay.

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1 Gorini P, Gapizzi FD A three-trocar approach to laparoscopic removal of the gallbladder. *Surg Laparosc Endosc* 1997; 7: 181–2.
2 Laws HL. Laparoscopic cholecystectomy utilizing two ports. *Surg Endosc* 1996; 10: 857–8.
3 Ng WT Three-port laparoscopic cholecystectomy *Surg Laparosc Endosc* (in press).

whose condition is too unstable to undergo major gastric surgery, or when localization of the bleeding proves difficult

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One-wound laparoscopic cholecystectomy

Letter 1

Sir

We read with interest the article by Dr Navarra *et al.* (*Br J Surg* 1997; 84: 695). The authors described a method of using two 10-mm trocars and three sutures passing through the abdominal wall. We are interested to know if the authors encountered any difficulty in dissection and the application of clips. The dissecting forceps are close to the telescope and dissection may have to be done with an end-on view and, although the sutures served to open up Calot's triangle, there was no direct counter-traction.

We described our method of performing laparoscopic cholecystectomy using only two ports[1] We use an operating telescope with a pair of long grasping forceps passing through the working channel. An 11-mm epigastric port is created for dissection and application of clips This port has subsequently been reduced to 5 mm with the development of 5-mm clip applicators. A percutaneous suture is used to retract the gallbladder laterally and cephalad. We have performed the procedure in 110 patients, 50 of whom were included in a prospective randomized trial[2]. We find that our method is comparable to standard four-port laparoscopic cholecystectomy in terms of safety, operation time (mean 69 min), postoperative stay and analgesics requirement. Our patients are more satisfied with the two-port method

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1 Leung KF, Lee KW, Cheung TY, Leung LC, Lau KW Laparoscopic cholecystectomy: two-port technique *Endoscopy* 1996; 28· 505–7.
2 Leung SK, Lee KW, Lau KW *et al* Two-port laparoscopic cholecystectomy, a prospective randomized trial *8th Overseas Meeting of Royal College of Surgeons of Edinburgh*, Hong Kong 1996 Abstract A4

Letter 2

Sir

We read with interest this paper detailing a method for one-wound laparoscopic cholecystectomy. Although the method has become the procedure of choice for patients with symptomatic gallstones[1], a recent systematic review concluded that doubts remain about the effectiveness and safety of this procedure when compared with open cholecystectomy[2]

One reason for this conclusion was the relative lack of validation from clinical trials of a standard technique for laparoscopic cholecystectomy. Given these concerns and the fact that in most units in the UK the technique is now relatively standard it seems unwise to introduce a technical modification that transgresses the principles established in open cholecystectomy

A bimanual technique allows the surgeon to maintain traction on Hartmann's pouch during Calot's triangle dissection and facilitates an operative cholangiogram The use of traction sutures instead of a grasping forceps is likely to lead to a degree of loss of fine control

Insertion of a straight needle into the gallbladder wall may be difficult if the patient is obese and manipulation of this straight needle within the gallbladder risks damaging portal structures. Insertion of sutures and the subsequent application of traction through these may lead to tearing of the gallbladder wall with consequent spillage of bile and gallstones into the peritoneal cavity.

The authors claim that the advantages include reductions in postoperative pain and inpatient stay Although it has been established that laparoscopic cholecystectomy is associated with less postoperative pain than the open procedure[2], it is not possible to state whether there is any further reduction in pain with their technical modification. The reported length of postoperative inpatient stay following one-wound laparoscopic cholecystectomy is similar to previously reported series of laparoscopic cholecystectomy[2].

Clearly, in the hands of Navarra and colleagues the procedure is feasible but the approach seems potentially unsafe and unless claims are substantiated by large scale clinical trials this technique should not be adopted.

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1 Sawyers JL Current status of conventional (open) cholecystectomy *versus* laparoscopic cholecystectomy *Ann Surg* 1996; 223· 1–3.
2 Downs SH, Black NA, Devlin HB, Royston CMS, Russell RCG. Systematic review of the effectiveness and safety of laparoscopic cholecystectomy *Ann R Coll Surg Engl* 1996; Part II. 241–322.

Author's reply

Sir

I would like to thank Mr Leung and colleagues and Messrs Powell and Siriwardena for their letters and to thank you for allowing us to reply to them

They express concern about the safety of dissection with our technique As you know the hinges of surgery are vision and traction, we think that both systems have to be independent A 10-mm trocar is used to insert a 10-mm laparoscope and sutures passing through the abdominal wall to retract the gallbladder. Mr Leung *et al.* use an operating telescope with a pair of long grasping forceps passing through the working channel We think that the solution adopted may lead to a freezing of the image as moving the forceps means inevitable change to vision

In our technique the telescope and the operative instruments are close and coaxial. This aspect causes some difficulties that have been overcome in the following way· the surgeon keeps a 30° telescope with the left hand and the operative instruments with the right one.

Traction in our technique is completely guaranteed using sutures. The difficulties encountered in the insertion of the sutures and the leakage of bile are real problems, but easily controlled by an experienced surgeon and an appropriate toilette The first suture is passed through the fundus of the gallbladder; it allows retraction laterally and cephalad. The other sutures positioned on the infundibulum allow traction and counter-traction on the inferior part of the gallbladder, in so doing exposing the anterior and posterior part of Calot triangle It is easy to understand why we call this procedure 'Muppet show-man' technique.

British Journal of Surgery 1997, 84, 1625–1627

Correspondence

The Editors welcome topical correspondence from readers relating to articles published in the Journal. Letters should be no more than 250 words in length and should be typed on A4-sized paper in double-spacing.

Laparoscopic fenestration of symptomatic non-parasitic cysts of the liver

Sir

Dr Fabiani and colleagues (*Br J Surg* 1997, 84: 321–2) support the use of laparoscopic fenestration of non-parasitic liver cysts based on a consecutive series of ten patients in whom there were no complications or recurrence during a median follow-up of 25·5 months. Although I share their enthusiasm for this technique it is not without reservation.

A 49-year-old woman, known to have a symptomatic right lobe liver cyst measuring 17 cm in diameter, presented with acute upper abdominal pain; computed tomography revealed that the cyst had ruptured (*Fig 1*). Laparoscopic fenestration was performed. The clear cyst fluid was found to be negative after cytology, parasitology and microbiology culture. A portion of cyst wall, 14 cm in diameter, was removed and confirmed as simple on histological examination; she made an uneventful recovery. For the first 4 months she remained asymptomatic then complained of upper abdominal 'tightness' and was found to have a recurrent cyst, 12 cm in diameter. Her symptoms and the cyst size have remained static for a period of 12 months.

Cyst recurrence may occur after extensive laparoscopic fenestration for a simple liver cyst, a situation which can occur rarely following open surgery[1] Patients should be warned of this possibility, and the indications for surgery for simple liver cysts should not be extended because of the laparoscopic approach

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1 Scott Jones R. Surgical management of non parasitic liver cysts In: Blumgart LH, ed. *Surgery of the Liver and Biliary Tract*. Edinburgh: Churchill Livingstone, 1990: 1025–32.

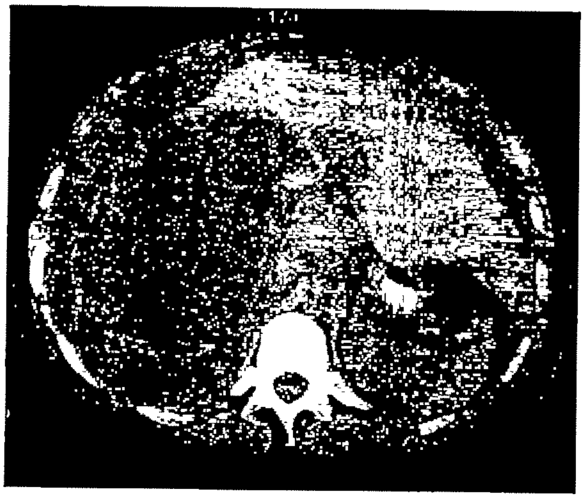

Fig. 1 Computed tomography demonstrating right lobe liver cyst and free intraperitoneal fluid due to cyst rupture

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Colour flow duplex imaging of occlusive arterial disease of the lower limb

Sir

We enjoyed the thorough review of Messrs Pemberton and London (*Br J Surg* 1997; 84: 912–19) of imaging modalities for lower-limb arterial disease (duplex scanning, arteriography and magnetic resonance imaging). We agree that duplex scanning, although user-dependent, has emerged as an extremely reliable tool and should presently be considered the gold standard. As the authors mentioned this is, in no small part, due to the skill and dedication of many vascular technologists around the country.

The review covered the usefulness of duplex scanning in verifying the efficacy of balloon angioplasty but the authors did not mention duplex surveillance of vein bypasses, especially in the few instances where a narrowed segment cannot be demonstrated by careful multiplanar arteriography. We have seen five patients with duplex-detected, angiographically invisible stenoses which were confirmed at operation and corrected surgically with good outcomes

We would therefore expand one of their conclusions: that duplex scanning should be considered the gold standard for imaging vein graft disease as well as occlusive arterial disease in the lower limb.

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Intragastric endoscopic surgery using the transanal endoscopic microsurgery technique

Sir

Dr Nakagoe and colleagues present a nice technique for intragastric endoscopic surgery (*Br J Surg* 1997; 84: 830). Endoscopic surgical techniques can be extremely useful in open gastric surgery as well Recently we performed an emergency operation on a patient with life-threatening gastric bleeding after a failed attempt to control the bleeding endoscopically. During operation we found a very large stomach and the fundus was hardly accessible. An anterior gastrotomy was performed and although it was possible to palpate the endoscopically applied haemostatic clips, it was impossible to visualize the bleeding ulcer We closed the gastrotomy with a purse-string suture. The oesophagus was controlled with a sling, and a non-crushing bowel clamp was applied to the distal stomach. A blunt-tip trocar and cannula was inserted into the stomach which was filled with gas. After insertion of a laparoscope the whole inside of the stomach was clearly visible and the bleeding ulcer was easily identifiable. The bleeding was controlled with an external suture. This 'open endoscopic' approach can be life-saving in patients kinase inhibitor) protects against neutrophil-mediated lung injury in a model of aortic occlusion (30 min) and reperfusion (120 min).

Sprague-Dawley rats were randomized into three groups: control ($n = 9$), ischaemia–reperfusion (IR, $n = 9$) and IR pretreated with herbimycin A (HerbIR, $n = 9$). Pulmonary endothelial permeability was measured by wet:dry lung weight ratio (W:D) and bronchoalveolar lavage protein concentration (BALprot). Lung neutrophil infiltration was measured by tissue myeloperoxidase activity (MPO) and bronchoalveolar lavage polymorphonuclear neutrophil count (BALPMN). Expression of HSP72 was measured in lung tissue by Western immunoblotting

	Control	IR	HerbIR
MPO (units) g^{-1})	2·9(0·46)	4·6(0·54)*	3·07(0·42)†
BALPMN (10^5 per ml)	0·83(0·25)	3·36(0·60)*	1·17(0·20)†
W:D	3·04(0·24)	4·24(0·21)*	3·94(0·15)*
BALprot ($\mu g\ m^{-1}$)	236·4(18·2)	289·1(42·3)	248·7(48·9)

Values are mean(s.e.m.). *$P < 0{\cdot}05$ *versus* control, †$P < 0{\cdot}05$ *versus* IR (analysis of variance with Student–Newman–Keuls multiple comparison)

IR resulted in acute lung injury with tissue oedema (W:D) and neutrophil infiltration (MPO, BALPMN). Herbimycin A, *in vivo*, induced HSP expression and attenuated neutrophil infiltration (MPO, BALPMN) In this experiment herbimycin A did not significantly reduce microvascular leakage (W:D, BALprot). Further studies are necessary to establish optimal dosage regimens.

Rac1-dependent pathway regulates cardiac cell morphology and hypertrophy in the neonatal rat heart

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Rac1, a member of the ras-superfamily of guanosine 5′-triphosphate (GTP) binding proteins, regulates a signal transduction cascade linking cell surface receptors to cytoskeletal re-organization. Because the signalling mechanisms underlying cardiac hypertrophy remain unclear, the present study examined the regulatory role of rac1 in cardiac morphology and hypertrophy.

Replication-deficient recombinant adenoviruses encoding either a constitutively active mutant (AdCArac1) or a dominant negative mutant (AdN17rac1) were constructed and used to infect cardiac monocyte (CM) primary cultures, which produced increased levels of rac1 expression as demonstrated by Western blot analysis. Unlike adenovirus infected controls (AdBgal), fluorescein–phalloidin staining demonstrated that AdCArac1 expression produced sarcomeric actin reorganization, the recognized phenotype of cardiac cell hypertrophy. Contractile apparatus alterations were identical to those induced by hypertrophic agonist (angiotensive II, phenylephrine, endothelin 1 and leukaemia inhibitory factor). In contrast, AdN17rac1 expression in CMs produced fragmentation of the sarcomeric actin and consistently disrupted actin reorganization in response to hypertrophic agonists.

Further support for the role of rac1 in regulating the hypertrophic response was obtained from biochemical studies which demonstrated the AdCrac1-increased [^{3}H]leucine incorporation (AdBgal 7707(154) c.p.m., AdCArac1 11 667(403) c.p.m; $P<0·0001$, t test), whereas AdN17rac1 expression decreased [^{3}H]leucine incorporation for all hypertrophic stimuli

The effects of rac1 on cytoskeletal reorganization and its ability to regulate protein synthesis bidirectionally suggest that rac1 is a critical component of the signalling cascade leading to cardiac hypertrophy. This also provides the first evidence for the convergence of receptor–G protein–tyrosine kinase signalling pathways with cytokine signal transduction through a common small GTP binding protein, rac1.

Human saphenous vein intimal hyperplasia is mediated via endothelin$_B$ receptors

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Up to 35 per cent of lower-limb saphenous vein grafts develop patency-threatening stenosis. The underlying pathology is intimal hyperplasia. There is increasing evidence that endothelin is an important mediator of intimal hyperplasia in human vascular tissue and it has recently been shown that endothelin acts via two receptors, $\mathrm{ET_A}$ and $\mathrm{ET_B}$ The purpose of this study was to investigate the role of these two receptor subtypes in the development of intimal hyperplasia in human saphenous vein. Experiments were conducted using an organ culture of human saphenous vein.

Segments of human saphenous vein were cultured for 14 days in medium supplemented with 30 per cent fetal calf serum, at 37 per cent, gassed with 5 per cent carbon dioxide. The experimental groups consisted of segments of vein from the same individual cultured in the presence of either an $\mathrm{ET_A}$ receptor (BQ123) or $\mathrm{ET_B}$ (BQ788) receptor antagonist. Both were used at a concentration of 3 μmol l^{-1}. The control group was cultured in the absence of either antagonist. After 14 days, neointimal thickness was measured using a computerized image analysis system The experiments were repeated ten times with each antagonist

The median (range) neointimal thickness of the control group for the BQ123 studies was 26 (13–56) μm compared with 25·5 (13–54) μm for the experimental group ($P=0·54$, Wilcoxon paired rank test). The neointimal thickness of the control group for the BQ788 studies was 28 (20–49) μm compared with 15·5 (4–49) μm for the experimental group ($P=0·036$). The $\mathrm{ET_B}$ antagonist therefore produced a 45 per cent reduction in neointimal thickness compared with only 2 per cent with the $\mathrm{ET_A}$ antagonist (although this was not statistically significant).

It is concluded that intimal hyperplasia in human saphenous vein is mediated via $\mathrm{ET_B}$ receptors and that $\mathrm{ET_B}$ receptor antagonists may have an important role to play in the amelioration of lower-limb vein graft stenosis

Arterial compliance and blood flow

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The compliance and elastic recoil of human arteries are responsible for the shape of the waveform and the reverse component of normal arterial flow. The effect of compliance on volume flow in human arteries is unknown The aim of this work was to produce artificial vessels that have similar elastic properties to human peripheral arteries.

Vessels were tested in a previously developed model of the lower limb circulation which is capable of generating pulsatile triphasic flow at a range of heart rates and blood pressures. Vessels were formed by painting liquid latex on to a plastic rod 0·7 cm in diameter. The number of coats applied controlled the compliance of the tube Compliance was measured by filling the vessel with water and measuring the volume change with increasing pressure. The compliance was calculated as the ratio between the changes in pressure and volume.

	No of coats applied		
	8	10	12
Compliance (μl mmHg^{-1} cm^{-1})	0·86	0·79	0·65

The volume flow in the model was measured using a Transonics transit time flowmeter, which is accurate to ±5 per cent of absolute flow.

	Volume flow (ml min^{-1})		
	VC 0·86	VC 0·79	VC 0·65
Heart rate			
60	481	372	364
70	641	481	408
80	728	568	481
100	918	845	612
120	1470	1250	1060

VC, vessel compliance (μl mmHg^{-1} cm^{-1}) $P=0·0045$ (VC 0·79 *versus* VC 0·86); $P=0·045$ (VC 0·65 *versus* VC 0·79); $P=0·0054$ (VC 0·65 *versus* VC 0·86) (paired t tests)

There was a significant reduction in flow in the more rigid vessels The results therefore indicate that atherosclerosis and vessel calcification are likely to compromise blood flow. This has important implications for both the prophylaxis and management of arterial disease

Herbimycin A attenuates ischaemia–reperfusion-induced pulmonary neutrophil infiltration

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Induction of heat shock proteins (HSPs) protects against cellular oxidant injury The aim of this study was to determine whether pharmaceutical induction of HSPs by herbimycin A (a tyrosine permeability, possibly by promoting oxidant-mediated cytoskeletal damage and/or metabolic inhibition

Photodynamic therapy for Barrett's oesophagus: a prospective randomized placebo-controlled trial

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Photodynamic therapy (PDT) is a form of cancer treatment in which cell damage is achieved by the action of light on a photosensitizing agent. It may also be of use in premalignant tissues such as Barrett's oesophagus To assess the value of this treatment, 32 patients with dysplastic Barrett's oesophagus were entered into a prospective double-blind placebo-controlled trial.

All patients were randomized to receive either the photosensitizing agent aminolaevulinic acid (ALA) at a dose of 30 mg kg^{-1} or placebo Some 4 h later, patients underwent endoscopy and administration of green laser light (514 nm) at a power density of 120 mW per cm^2 for 500 s (i e. total energy 60 J). All treatments were performed under intravenous sedation as day cases. All patients were treated with omeprazole 20 mg daily. Endoscopy was repeated at 1 and 6 months to assess the effect of treatment.

In the group receiving ALA, a response was seen in 14 of 16 patients, with a mean decrease in columnar epithelial area of 30 (range 0–60 per cent) In the placebo group, a small decrease in area of Barrett's oesophagus was observed in two patients (mean 2 (range 0–10 per cent). This difference was statistically significant ($P<0·001$). No side-effects were observed in either group.

This is the first controlled trial of PDT in the treatment of Barrett's oesophagus. ALA-induced PDT provides safe and effective ablation therapy for Barrett's oesophagus. The role in prevention of progression to adenocarcinoma requires further study

Smoking-induced endothelial dysfunction, a primary feature of atherogenesis, can be reversed by the amino acid taurine

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Aims Endothelial dysfunction is an important early feature of atherogenesis Cigarette smoke, representing a major source of free radical stress, has been implicated in this disease process. Recently, a non-invasive technique using B-mode ultrasonography to measure brachial artery diameter has been described for evaluation of flow-dependent endothelial relaxation, a feature that has been shown to be dependent on intact endothelial function Using this technique, it was demonstrated that chronic cigarette smoking is associated with loss of endothelial relaxation It is postulated that the reported impaired endothelium-dependent arterial dilatation may be a reflection of a chronic imbalance between oxidants and anti-oxidants, and a decrement in endothelial nitric oxide availability To test this hypothesis, the effect of oral supplementation of the known potent antioxidant vitamin C and the amino acid taurine, which has antioxidant properties, and has also recently been shown to upregulate constitutive nitric oxide production, were investigated and compared

Methods A study was made of 20 healthy smokers, with a self-reported smoking history of 2 pack-years, and 15 control non-smoking subjects Using ultrasonography, brachial artery diameter at baseline conditions and during reactive hyperaemia was measured. The smoking group was rescanned after antioxidant supplementation: vitamin C, taurine 1·5 g per day for 5 days.

Results Flow-mediated dilatation was observed in all control subjects, but was significantly impaired in smokers ($P<0·005$) Oral supplementation of vitamin C had some effect on flow-mediated dilatation ($P=0·65$). In contrast to this, oral supplementation of taurine markedly improved dilatation ($P=0·005$), returning diameters to those of controls.

	Flow-dependent dilatation (mm)
Non-smokers	0·37(0·09)
Smokers	0·025(0·01)
Smokers	
No treatment	0·02(0·02)
Vitamin C	0·12(0·04)
Taurine	0·36(0·04)

Values are mean(s d.)

Conclusion This study confirms that chronic cigarette smoking is associated with impairment of endothelium dependent relaxation It highlights the use of the measurement of a physiological parameter (flow-mediated dilatation) as a possible future diagnostic tool for endothelial dysfunction and atherogenesis The amino acid taurine has the capability to restore endothelial function Importantly, it may have a therapeutic role in the management of smoking-related arterial disease.

Contrast echocardiography: confirmation of patency of laser channels after transmyocardial laser revascularization

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Objective Transmyocardial laser revascularization is known to reduce angina in patients with endstage coronary artery disease. However, up to now there has been no reliable method to confirm the patency of laser channels in the beating heart

Methods By means of a 1000-W carbon dioxide laser channels were drilled into the ischaemic myocardium Complete wall penetration was detected by TEE The patients underwent concomitant coronary artery bypass grafting when necessary Myocardial contrast echocardiography (C-Echo) was performed after different time intervals. In brief, 6 ml of echo contrast medium (ECM) was injected by means of a catheter into the left ventricle. The myocardial distribution of the ECM was visualized by TEE or transthoracic echocardiography

Results Within a 16-month period, 38 patients have had laser treatment Of these, 15 patients have been investigated after a mean(s.d.) 6·7(4·4) (range 2–14) months. C-Echo could demonstrate (mean(s.d) 2–5(1·3) patent laser channels in the apical or supra-apical area in each case. In phase I the channels were perfused from within the left ventricle during systole Phase II showed the subsequent dispersion of ECM in the subendocardium lasting about ten beating cycles. In phase III ECM was washed out via the native coronary vein system. When the ECM was injected into the bypass or the native coronary arteries, the laser channels did not drain into the cavity Angina New York Heart Association class improved from grade 4 to 2 in four patients, from grade 4 to 1 in three, from grade 3 to 2 in two and from grade 3 to 1 in six.

Conclusion This is the first study demonstrating long-term laser channel patency in the beating heart and confirming blood supply via the channels to the adjacent myocardium during systole. Demonstration of open channels probably predicts improvement of symptoms.

hyperdynamic circulation following partial portal vein ligation (PPVL). This suggests that increased synthesis of TNF-α is central to the pathogenesis of the circulatory changes following PPVL. The actions of TNF-α are regulated by activation of the nuclear transcription factor NF-κB, which regulates gene transcription of several proinflammatory cytokines as well as inducible nitric oxide synthase. Activation of NF-κB can be inhibited by antioxidants such N-acetycysteine (NAC) *in vitro*. In this study the hypothesis that administration of NAC blocks the development of a hyperdynamic circulation following PPVL has been tested.

PPVL and sham controls were studied at 14 days. Mean(s.e.m.) cardiac index increased from 18·8(1·3) to 28·4(1·5) ml min^{-1} 100 g^{-1} ($P<0\cdot05$), systemic vascular resistance decreased from 7·0(0·6) to 3·5(0·3) mmHg ml^{-1} per min per 100 g ($P<0\cdot05$) and portal pressure increased from 9·0(0·7) to (14·7)(1·1) mmHg ($P<0\cdot05$) following PPVL. Administration of NAC completely blocked the above haemodynamic changes such that values obtained were no longer different from those in sham controls.

It is concluded that administration of NAC completely reverses the hyperdynamic circulation following PPVL. The mechanism of action is unknown but is likely to involve inhibition of TNF-α-activated pathways mediated by NF-κB.

Prognostic power of Child–Pugh grading on admission or after recovery following acute variceal haemorrhage

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Child–Pugh classification grades patients with increasingly severe liver disease into A, B or C depending on routine clinical and laboratory measurement of encephalopathy, ascites, serum bilirubin and albumin concentration, and prothrombin time. During admission for variceal haemorrhage values may change, as may Child–Pugh grading. It is not known when Child–Pugh grading is most predictive of early and long-term survival, so a prospective study has been conducted to evaluate the usefulness of this system.

A total of 161 patients were admitted with a first variceal haemorrhage from cirrhotic portal hypertension between 1984 and 1993 inclusive. Child-Pugh grade was calculated on admission in all patients, and at 6 weeks in those who survived. Management was standardized throughout the period of the study, using endoscopic sclerotherapy as first-line treatment, and close long-term follow-up. Survival analysis was conducted using Kaplan–Meier plots with log rank testing and χ^2 testing for trend.

Forty-eight patients died during the first inpatient admission, while 13 died during an early second admission for acute variceal haemorrhage. Of the remaining 100 patients, 31 remain alive, 36 died from the complications of cirrhosis and 33 were lost to follow-up. Child-Pugh grading on first admission was strongly predictive of survival during the first inpatient episode, with the death of two of 14 patients graded A, seven of 77 with grade B, and 39 of 70 with grade C (χ^2 for trend, $P<0\cdot001$). Grading on first admission was not predictive of subsequent long-term survival in patients under long-term follow-up, with death in eight of 12 patients graded A, 12 of 21 graded B, and 15 of 30 graded C ($P<0\cdot99$, log rank test), whereas grading at 6 weeks was predictive of long-time survival with death in nine of 30 patients graded A, 21 of 30 graded B, and seven of seven graded C ($P=0\cdot0001$). Child–Pugh grading at 6 weeks improved over that on first admission in 36 patients (14 from grade C to B, 11 from grade B to A, and 11 from grade C to A) and worsened in six (five from grade A to B, one from grade B to C).

It is concluded that the timing of Child–Pugh grading is crucial to the determination of early and long-term prognosis following a first variceal haemorrhage from cirrhotic portal hypertension. Grading on admission predicts early but not long-term survival, whereas grading after recovering at 6 weeks predicts long-term survival. Those who remain Child–Pugh grade C after recovery are in imminent danger of death and should be considered as candidates for early liver transplantation.

Peroxynitrous acid increases junctional permeability in human intestinal epithelial mono layers: role of the amiloride-sensitive Na + –H + antiport

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Nitric oxide (NO) can react with superoxide ($O_2^-\bullet$) to form peroxynitrite ($ONOO^-$) which, if protonated to peroxynitrous acid (ONOOH), can further decompose, forming hydroxyl radical ($OH\bullet$): $O_2^-\bullet + NO \rightarrow ONOO^-$; $ONOO^- + H^+ \leftrightarrow ONOOH \rightarrow OH\bullet + NO_2$. It was hypothesized that the deleterious effects of $NO\bullet$ on gut epithelial hyperpermeability are caused by ONOOH

Caco-2_{BBe} cells growing on permeable supports were incubated in medium without HCO_3^- for 24 h. Permeability was assessed by measuring the apical to basolateral clearance (nl cm^{-2} h^{-1}) of fluorescein sulphonic acid (mol.wt.478 Da).

The $NO\bullet$ and $O_2^-\bullet$ donor, SIN-1, dose dependently increased permeability The addition of amiloride 500 μm (Na^+–H^+ antiport blocker) exacerbated the hyperpermeability induced by SIN-1 2 mmol l^{-1} The hyperpermeability induced by SIN-1 plus amiloride was ameliorated by addition of deferoxamine 5 mmol l^{-1} ($ONOO^-$ scavenger), mannitol 100 mmol l^{-1} or dioxymethylsulphoxide 25 mmol l^{-1} ($OH\bullet$ scavengers), or ascorbate 250 μmol l^{-1} (ONOOH scavenger) (*Figure*). Mean(s.d.) cellular adenosine 5′-triphosphate levels were decreased synergistically to 68·8(2·9) per cent of control levels by SIN-1 plus amiloride. Confocal fluorescence microscopy using rhodamine–phalloidin showed marked disruption of the normal perijunctional F actin distribution by SIN-1 plus amiloride.

It is concluded that inhibition of the NA^+–H^+ antiport lowers intracellular pH, promoting protonation of $ONOO^-$ to ONOOH Either ONOOH or $OH\bullet$ increases perijunctional

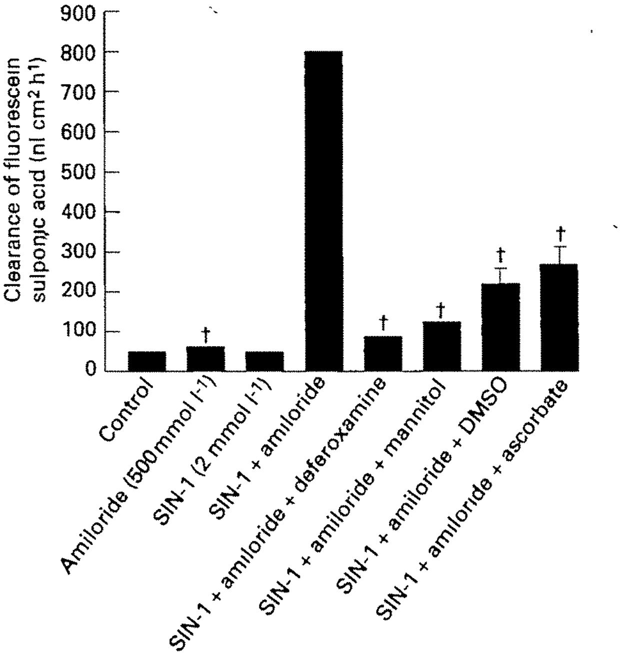

Fig. 1 Clearance of fluorescein sulphonic acid. *$P<0\cdot01$ *versus* control; †$P<0\cdot01$ *versus* SIN-1 plus amiloride (analysis of variance with Tukey's test)

associated with an early circulating neutrophilia followed by neutropenia. It was hypothesized that patients who developed MOF after major injury would have different circulating neutrophil counts than patients without MOF.

Venous blood was sampled from 33 high-risk trauma patients (Injury Severity Score greater than 15) at 0 (within 30 min of injury), 3, 6, 12, 24, 48, 72, 96 and 120 h, and a differential count was performed on a Coulter STKS machine. The normal range for circulating neutrophils was $2-7 \times 10^6$ per ml. Patients were assessed daily from day 3 for major infection (wound, pneumonia, abdominal abscess) and MOF. Values are given as mean(s.e.m.); analysis was by analysis of variance (ANOVA) and multivariate regression (SPSS 6·12).

Twelve patients developed a major infection, of whom seven also developed MOF. Neutrophil counts varied from normal to above normal throughout the 5 days and reached significant peaks at 3 h (13·9(1·2) and 24 h(10·3(0·8)) after injury related to delayed-onset MOF and infection respectively (*P*0·015).

Table 1 Neutrophil counts in patients with and without MOF

	Time after injury (h)								
	0	3	6	12	24	48	72	96	120
MOF ($n=7$)	12	15	6	4	9	4	6	6	12
No MOF ($n=26$)	5	14	8	9	11	10	10	8	8

Circulating neutrophil numbers after injury show marked variability. Early neutrophilia followed by neutropenia at 12 h correlated with a poor outcome. This pattern may indicate a different early neutrophil kinetics that renders some injured patients at risk for infection and/or development of MOF.

Perioperative nimodipine reduces the requirements for anaesthetics and analgesics and the incidence of opioid-related side-effects

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Background and study objective Several studies have shown that peripheral tissue injury provokes prolonged peripheral sensitization and hyperexcitability of spinal neurones. Recent studies imply, however, that postoperative hyperalgesia is not dependent solely on nociceptive inputs during surgery, but also on inputs from the wound after surgery. Preliminary data in humans suggest that intravenous nimodipine, a calcium channel antagonist, enhances the analgesic effects of morphine.

Study design The study was prospective, randomized, double-blind and placebo controlled.

Materials and methods Forty-five patients classified as American Society of Anesthesiologists grade I–II (aged 20–63 years), undergoing cholecystectomy, were assigned to three treatment groups ($n=15$): group 1 received intravenous nimodipine in a dose of $6\,\mathrm{mg\,h^{-1}}$ 1 h before operation up to the end of the operation, followed by a dose of $2\,\mathrm{mg\,h^{-1}}$ for the first 24 h after operation. Group 2 received placebo up to 30 min after the start of operation and thereafter nimodipine in the same dose as group 1. Group 3 received placebo over the operative period. Anaesthesia (T_0) was induced with propofol $2{\cdot}5\,\mathrm{mg\,kg^{-1}}$ atracurium $0{\cdot}6\,\mathrm{mg\,kg^{-1}}$ and alfentanil $7\,\mu\mathrm{g\,kg^{-1}}$ and was maintained with propofol $2\,\mathrm{mg\,kg^{-1}h^{-1}}$ atracurium $5\,\mu\mathrm{g\,kg^{-1}min^{-1}}$ and 66 per cent nitrous oxide in oxygen. During operation increased blood pressure (BP) or heart rate (HR) (more than 10 per cent above T_0) not responding to additional intravenous propofol (20-mg bolus) was treated with an additional 20-mg propofol bolus together with 1 mg alfentanil intravenously. After operation patients received morphine sulphate intravenously until comfortable. A morphine patient-controlled analgesia (PCA) pump was then commenced with a demand dose of 1·5 mg and a lockout of 6 min. Measurements included non-invasive BP, HR, $\mathrm{SP_{O_2}}$ and administration of supplemental propofol and alfentanil. Pain assessment was made using visual analogue self-rating 100-mm scale for 48 h. Statistical analyses was performed using one-way analysis of variance followed by *post hoc* tests and the Mann–Whitney *U* test.

Results Perioperative administered nimodipine during operation (group 1) significantly decreased intraoperative need for anaesthetics (propofol) and analgesics (alfentanil) by 82 and 90 per cent respectively compared with placebo ($P<0{\cdot}001$), whereas when nimodipine was administered followed by surgical incision (group 2) it decreased propofol and alfentanil requirement by 47 and 39 per cent respectively ($P<0{\cdot}05$). Group 1 patients experienced less pain compared with both group 2 and placebo-treated patients ($P<0{\cdot}001$) for the first 48 h after operation. Group 1 patients self-administered significantly less morphine by PCA in the first 24 h after surgery (mean(s.d.) 32(8·5) mg) compared with both placebo (75)(15) mg $P<0{\cdot}001$) and group 2 (59(13) mg, $P<0{\cdot}001$) treated patients respectively. Concomitantly and during the first 24 h postoperation, fewer opioid-related side-effects (urinary retention) were observed in group 1 patients (none of 15) *versus* four of 15 in group 2 ($P<0{\cdot}01$) and nine of 15 (in group 3 ($P<0{\cdot}001$).

Discussion These results are of major clinical importance, as they suggest that nimodipine has a strong pre-emptive effect and reduces opioid-related side-effects. When nimodipine is given after the surgical stimulus, it enhances PCA with morphine. This study lends further support to more extensive use of nimodipine during operation.

Effect of the presence of p53 protein on patient survival in gastric cancer

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Sixty-seven patients with gastric cancer had immunohistochemical staining of tumour tissue for p53 protein. Five died in the immediate postoperative period. The mean age of the remaining 62 patients was 54·7(13·9) years, 36 were men and 26 were women. Thirty-five patients were p53 positive and 27 were p53 negative. Twenty-nine had either non-curative surgery or no surgery. Thirty-three patients had potentially curative surgery of whom 13 are still alive. Patients undergoing curative surgery had lower stage tumours and lived longer (mean(s.d.) 2·4(0·8) and 37·2(32·0) months) than those having non-curative or no surgery (3·9(0·3) and 9·7(19·6) months). Information on time to recurrence was available for 33 patients who had undergone potentially curative surgery; the mean(s.d.) of 42·4(38·5) months in the p53 negative group ($n=17$) was not significantly greater than that of 25·13(21·5) months in p53 positive patients ($n=16$). Irrespective of treatment, survival was significantly longer in p53-negative patients (36·5(39·7) *versus* 14·9(14·7) months; $P<0{\cdot}05$, log rank test). All p53 patients died within 3 years. Six p53-negative patients were alive after 3 years and three lived for more than 5 years. These data support the hypothesis that failure to express mutant p53 protein imparts a survival advantage to patients with gastric cancer.

N-acetylcysteine abrogates the hyperdynamic circulation in partial portal vein-ligated rats

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Recent studies have shown that infusion of anti-tumour necrosis factor (TNF) antibodies block the development of the a major component of the resolution phase of ARDS, produced by basic fibroblast growth factor in a rat aortic ring model.

Taken together, these data support the involvement of mob-1 in the development of ARDS, conceivably through chemotactic actions on inflammatory cells and modulation of angiogenesis in the recovery phase of the disease.

Expression of endothelin 3 and its receptor in Hirschsprung's disease

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Background In recent years some unexpected genes have been implicated in the pathogenesis of Hirschsprung's disease (HD). These code for molecules previously thought to be involved only with blood pressure control: endothelin (ET) 3 and its receptor endothelin B receptor (EDNRB). No data exist as to the cellular role of these molecules in the development of HD.

Aim The aim was to assess levels of gene expression of ET-3 and EDNRB in patients with Hirschsprung's disease.

Study design Total RNA was extracted from ganglionic and aganglionic specimens from ten patients with HD (eight short segment, one long segment, one total colonic) and form colonic specimens from ten age-matched control patients with non-gut motility-related disorders. A reverse transcriptase–polymerase chain reaction method was developed to study relative amounts of messenger RNA (mRNA) to ET-3 and EDNRB within each group using expression of a housekeeping gene known to be expressed at a constant level (GAPDH) as a control.

Results Levels of ET-3 mRNA in the ganglionic and aganglionic gut segments of patients with HD were significantly lower than those of control specimens ($P<0{\cdot}05$). In patients with HD there was no difference in ET-3 mRNA levels between ganglionic and aganglionic segments. There was no difference in EDNRB mRNA levels between the ganglionic and aganglionic segments of patients with HD and controls, with again no difference between paired ganglionic and aganglionic segments.

Conclusion ET-3 gene expression is effectively downregulated in HD compared with that in controls. This appears to be irrespective of the causative gene mutation, suggesting interaction between ET-3 and other factors such as ret protein during neural crest colonization of the distal gut. The finding of ET-3 downregulation within the proximal ganglionic segment is additional evidence that the proximal gut is abnormal in HD and may explain the high frequency of gut motility disorders seen in these infants.

Primary wound closure produces superior results compared with laying open of pilonidal sinus

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Treatment of pilonidal sinus can be complicated by slow healing with regular dressings of unhealed wounds over many months. Resection with primary skin closure offers healing within 2–3 weeks but with a risk of wound breakdown and prolonged delay in healing, whereas laying open of the pilonidal tract leaves an open wound to heal slowly.

Inpatient stay and time to healing were compared in 90 patients with pilonidal sinus treated either by wide skin excision and asymmetrical primary closure (Karydakis procedure) carried out by one surgeon or by laying open. Follow-up was from outpatient clinic records, and from patient and general practitioner questionnaires.

	Primary closure ($n=41$)	Lay ($n=49$)	*P*
Hospital stay (days)*	7 (6–8)	2 (1–2)	<0·0001†
Interval from operation to cessation of dressings (weeks)*	3 (3–6)	6 (4–8)	0·0009‡
Unhealed at 10 weeks after operation	0	8	0·013§
Recurrence	0	5	0·100§

*Values are median (interquartile range). †Mann–Whitney *U* test, ‡log rank test; §χ^2 test

Excision with primary closure resulted in a shorter period with dressings and fewer unhealed wounds, but involved a longer hospital stay compared with laying open. Primary wound closure after pilonidal sinus excision produced superior results. Despite greater hospital cost, patients should be managed with primary closure by a suitably experienced surgeon.

Antegrade transport of leukaemia inhibitory factor down nerves

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The results following peripheral nerve repair in adults, despite advances in microsurgical techniques, are generally poor due in part to neuronal death, inadequate regeneration of axons across the repair site, incomplete end-organ reinnervation and muscle atrophy. Leukaemia inhibitory factor (LIF) has been shown to improve motor and sensory neural survival in culture, and to enhance regeneration of damaged skeletal muscle. It is the authors' hypothesis that *in vivo* it may also decrease the above causes of dismal repair results.

Previous work at our institute by Donato, Leong and Tham using the rat sciatic nerve model has shown elegantly that LIF injected at the repair site does improve axonal regeneration, while at the same time protecting deinnervated muscles from atrophy. This suggests strongly that LIF is transported in an antegrade fashion down degenerating nerve axons. The purpose of this study was to demonstate whether, how and when this antegrade LIF transport occurs. Using the same rat model, transected sciatic nerve ends were entubulated using silicone cuffs filled with ^{125}I-radiolabelled LIF. At time intervals of up to 1 week the distal nerve and representative muscle samples were assessed to establish the distribution of radioactivity.

LIF was found to collect preferentially in deinnervated muscles supplied by the sciatic nerve; this occurred as early as day 1. It did appear to get there by antegrade neural transport, although this was not clear. To confirm this, the nerve between the entubation site and muscle was ligated, to block this mode of transport should it be present. From this, it appears likely that in addition to significant antegrade LIF transport there is a smaller systemic component due mainly to upregulation of LIF receptors on deinnervated muscles. Subsequent studies are planned to highlight whether this antegrade LIF transport is an active process, or simply due to diffusion.

Early neutrophil counts after trauma relate directly to delayed infection and multiple organ failure

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Neutrophil kinetics after injury play a crucial mechanistic role in multiple organ failure (MOF). Animal studies have shown that neutrophil sequestration and end-organ injury after trauma are

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Effect of CD4$^+$ and CD8$^+$ cell depletion on wound healing

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T cells are thought to modulate wound healing by the release of lymphokines which act on fibroblasts both directly and via macrophages to effect collagen production and maturation The effect of depleting CD4$^+$ and CD8$^+$ lymphocytes in an animal model on the resulting biomechanical properties of healing laparotomy wounds was examined.

Some 128 PVG rats were thymectomized and randomly assigned to four groups of 32 animals. Rats were injected with either depleting doses of monoclonal antibody anti-CD4 (MRC OX38), anti-CD8 (MRC OX8) or saline The efficacy of the T-cell depletion was verified both before laparotomy and at killing by flow cytometry using fluorescent antibodies anti-CD4-PE (MRC OX35) and anti-CD8β-FITC (clone 341). Laparotomy was carried out and the wounds closed with a continuous 3/0 monofilament suture; the skin was closed separately with a 5/0 monofilament suture. Wounds were harvested at 10 weeks and examined by tensionometry to give values of ultimate strength, resilience (energy absorbed to elastic limit), toughness (total energy absorbed before rupture) and extension to the breaking point.

	Control group	CD4-depleted group	CD8-depleted group	CD4 and CD8-depleted group
Ultimate strength (N)	16·9(0·58)	13·7(0·47)*	20·8(0·61)*	18·3(0·62)
Resilience (10^{-3} J)	44·8(2·5)	25·3(1·4)*	54·2(2·8)*	31·5(1·8)*
Toughness (10^{-3} J)	157·2(5·2)	103(5)*	173·9(5·8)*	137·3(6·0)*
Extension (mm)	20·17(0·49)	16·94(0·58)*	19·75(0·65)	18·19(0·56)*
Elasticity constant (N mm^{-1})	3·49(0·17)	3·78(0·19)	4·78(0·33)*	5·77(0·33)*

Values are mean(s.e.m.) *($P<0·05$ two-sample *t* test)

Depletion of CD4$^+$ T lymphocytes decreased the ultimate strength, resilience and toughness, and conversely depletion of CD8$^+$ T lymphocytes increased the ultimate strength, resilience and toughness of a healing laparotomy wound in a rat This demonstrates that the subsets CD4$^+$ and CD8$^+$ T lymphocytes modulate the healing of a laparotomy wound in rats and therefore suggests that patients with a low CD4 count or decreased CD4 function will heal wounds poorly

Induction of heat shock protein 32 gene expression: a potent mechanism of tissue protection in ischaemic skin flaps

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Introduction Necrosis of pedicled skin flaps continues to be an important problem in reconstructive surgery. The main cause for tissue necrosis is insufficient microvascular perfusion with consequent hypoxia. Stress conditioning by heat shock has been shown to induce tolerance against a second injury The aim of this study was to investigate the role of heat shock protein (HSP) 32 in the maintenance of microcirculation and the modulation of skin flap necrosis in the context of the complex heat shock response.

Methods The skin flap model in the ear of the homozygous hairless mouse (8–10 weeks old, 24–30 g body-weight) was used To stimulate a single pedicle flap, the ear was incised through four-fifths of its base, leaving the anterior neurovascular bundle with a small portion of surrounding tissue acting as a single pedicle. Over 5-day period skin flap necrosis of 30–40 per cent of the whole flap area develops. The animals were divided into three groups ($n=6$). In groups 1 and 2 heat shock priming was induced by local heating (42·5–43°C) of the ear for 30 min 24 h before skin flap creation Group 2 received Sn-protoporphyrin IX (SnPP) 50 μmol kg^{-1} a potent inhibitor of HSP32, additionally. The third group (non-treated animals) served as control. Protein and gene expression of HSP32 were studied by immunohistochemical staining and Wester blotting. Microvascular perfusion in the proximal, central and distal part of the flap was assessed 1 day before and daily after flap creation over a 5-day period by laser Doppler flowmetry (LDF). Simultaneously, skin flap necrosis was evaluated by intravital fluorescence microscopy after intravenous injection of FITC–dextran (0·15 ml, mol.wt 150 000).

Results Heat shock priming resulting in a widespread induction of HSP32 as confirmed by immunohistochemistry. Simultaneously mean(s.d.) microvascular perfusion was significantly improved in group 1, compared with that in controls and mice that received SnPP, in particular in the distal parts of the single pedicle flaps (group 1 65(9·7) per cent, group 2 37(6·6) per cent, group 3 18(9·8) per cent (LDF, percentage of baseline)). Finally, tissue necrosis in group 1 was reduced to 14(2·6) on day 5, compared with 47(5·4) per cent in controls (group 3, $P<0·01$) and 53(9·5) per cent in mice in which HSP32 activity was inhibited by SnPP (group 2, $P<0·01$)

Conclusion Stress conditioning by heat shock priming improves microvascular perfusion and acute skin flap survival. These data suggest that induction of HSP32 is a potent mechanism for tissue protection, probably by modulation of vascular tone and reduction of oxidative cell damage.

A novel mediator of adult respiratory distress syndrome

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The authors have recently used differential display reverse transcriptase–polymerase chain reaction to identify mob-1, the novel rat homologue of the human α-chemokine IP-10, as a highly inducible gene in adult respiratory distress syndrome (ARDS) (IL-2-induced) lungs The present study aimed further to implicate mob-1 in the pathogenesis of ARDS. To that end, mob-1 mRNA upregulation was confirmed and localized to pulmonary macrophages using *in situ* hybridization and Northern blot analysis in two unrelated rat models of ARDS (IL-2 administration and coinfusion of lipopolysaccharide and platelet-activating factor) Furthermore, mob-1 was produced recombinant in *Escherichia coli* cells and tested for its properties in relation to lung injury

In vivo, intratracheal injection of mob-1 (50 μg per rat) induced leucosequestration in lung tissue (myeloperoxidase mean(s.d.) +93(8) per cent, $P<0·01$), the hallmark of ARDS, with preferential accumulation of polymorphonuclear neutrophils in bronchoalveolar lavage fluid (36(1) per cent *versus* 0·1(0·1) per cent in controls, $P<0·01$). *In vitro*, transwell migration studies demonstrated chemotactic activity of mob-1 towards human monocytes (+151(34) per cent *versus* mob-1 vehicle, $P<0·01$). *Ex vivo*, recombinant mob-1 exerted a very potent inhibitory effect (21(6) per cent of control value, $P<0·01$) on angiogenesis, proximal AP-1–CRE promoter element. These results suggest a regulatory role for the Src signalling pathway *NT/N* expression and underscore the possibility that tissue-specific endocrine gene expression in the gut may be subject to regulation by Src.

Optimal educational techniques for surgical trainees: 'lessons' from education theory

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Recent changes in surgical training have led to a reduction in 'in-service' education and a proliferation of courses for basic surgical trainees. Education theory has established four basic learning styles: accommodative, convergent, divergent and assimilative. These consist of contributions from an individual's preference for abstract conceptualization, concrete experience, reflective observation or abstract experimentalization. Learning styles are generalized within professional groups and the teaching method can therefore be tailored to achieve optimal results.

Basic surgical trainees (BSTs) were instructed to complete a previously validated learning style inventory. The questionnaire contained 'dummy' questions to prevent interpretation and modification of responses. The investigators were blinded to the individual trainee's results.

Thirty BSTs were assessed (mean age 27 (range 25–30) years. The median (interquartile range) learning style inventory scores were: concrete experience 13 (9–15), reflective observation 12 (10–13·5), abstract conceptualization 16 (12–19) and active experimentation 19 (15·75–21·25). The resultant distribution of individual preferred learning styles was: convergent, 20; accommodative, seven; assimilative, two; and divergent, one.

The optimal learning style for the majority of BSTs is accommodative or convergent. Both these styles rely heavily on active involvement in the learning process, 'hands on' experience and problem solving.

This is the first objective psychological assessment of the preferred learning styles of BSTs and training courses should be designed accordingly if they are to provide effective surgical education.

Endothelin 1 causes mucosal injury in the rat small intestine acting via ET_A receptors

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Aims The intestinal mucosa is highly susceptible to ischaemia–reperfusion and represents a primary target site during low-flow states such as septic or haemorrhagic shock. Raised levels of circulating endothelin (ET 1) have been reported during experimental and clinical haemorrhage or sepsis, indicating that the potent vasoconstrictor might contribute to the development of mucosal injury in these conditions. In the present study the influence of exogenous ET-1 on small intestinal mucosa and mucosal microcirculation was investigated. Further, the role of the ET_A and ET_B receptor subtypes in mediating the effects of exogenous ET-1 was determined.

Methods In anaesthetized Sprague-Dawley rats ET-1 3 nmol kg^{-1} was infused intravenously to achieve an approximately twofold increase in circulating ET-1 levels (group 1). In groups 2, 3 and 4, the animals were pretreated with the novel ET_A receptor antagonist ETR-P1/F1 peptide or the selective ET_A and ET_B receptor antagonists, BQ 610 and IRL 1038, respectively. Sham-operated animals served as controls (group 5). Mucosal thickness was measured using an image analysis system and the degree of mucosal damage was evaluated according to the Chiu scale. Using intravital fluorescence microscopy, mucosal microcirculatory changes in response to exogenous ET-1 were determined. The following parameters were assessed. (1) functional capillary density (FCD) and (2) red blood cell velocity (RBCV) in small intestinal mucosa. Measurements were performed at baseline conditions as well as 30 and 90 min after infusion of ET-1.

Results Intravenous infusion of ET-1 3 nmol kg^{-1} was associated with considerable mucosal injury and induced a significant reduction of mucosal thickness. In parallel, mean(s.d.) FCD of intestinal villi declined from 890(40) cm cm^2 (baseline conditions) to 589(36) and 521(24) cm cm^2 30 and 90 min after administration of ET-1, respectively, with a concomitant decrease in villus capillary RBCV. ET_A receptor blockage with ETR-P1/F1 peptide and BQ 610 prevented mucosal damage and ET-induced capillary perfusion failure. In contrast, pretreatment with ET_B receptor antagonist IRL 1038 was not effective in preventing ET-1-induced mucosal and microvascular injury.

Conclusion Acting via the ET_A receptor, raised levels of circulating ET-1 may contribute to the haemorrhagic or septic shock. Antagonism to the vasoconstriction-mediating ET_A receptor might therefore attenuate mucosal injury during low-flow states.

Fas is involved in reperfusion injury in the brain

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Stroke is a common disease caused by inadequate blood supply to areas of the brain. Current therapeutic options are being devised to enable the return of blood flow to the ischaemic region. However, reperfusion of previously ischaemic tissue can cause exacerbation of cellular injury. It has been shown in the brain that reperfusion injury causes death by apoptosis in the area surrounding the central necrosis[1] Some degree of apoptosis also occurs in ischaemic injury alone.

Fas, a member of the tumour necrosis receptor family, is known to be important in the control of apoptosis. Fas is activated by the binding of its ligand, Fas ligand, to induce apoptosis. The aim of this study was to investigate the role of Fas in reperfusion injury in the brain.

Rat embryos at day 20 of gestation were removed by caesarean section under sterile conditions. The brains were removed, dissected clear from the meninges and the neuronal cells cultured. After 7 days, the cultures were subjected to varying times of hypoxia and reoxygenation. Cells were then harvested and RNA was extracted. Northern blotting showed upregulation of Fas (mRNA) after periods of ischaemia alone and reoxygenation.

A model of focal cerebral ischaemia in the rat brain was also utilized[2]. A fine nylon suture was inserted a prescribed distance via the internal carotid artery of the rat to occlude the origin of the middle cerebral artery. The suture was then withdrawn to allow reperfusion. *In situ* end labelling of DNA fragmentation confirmed the presence of apoptotic cells in the damaged side of the brain. Expression of Fas mRNA and Fas protein were increased in the damaged side. It appears that Fas and, therefore, probably its ligand are involved in reperfusion injury in the brain, and this may potentially lead to further therapeutic options.

References

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These results demonstrate that the prevalence of *REG* expression in normal-appearing mucosa sampled close to the edge of colorectal carcinoma closely parallels that in tumour tissue itself, and differs significantly from mucosa sampled from more distant sites. These data are consistent with a hypothesis that *REG* expression is a feature of a proliferative mucosa at increased risk of malignant transformation rather than a molecular change acquired by a cell undergoing malignant change.

Evidence for different mechanisms for tumour growth following liver resection and transplantation

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Despite more radical tumour clearance, liver transplantation is associated with higher rates of tumour recurrence than liver resection. The effect of liver transplantation and resection on the growth of a colorectal cancer cell line was investigated in an attempt to examine the links between cancer regrowth, hepatocyte growth factor (HGF) and immunosuppression, using immunosuppressed and non-suppressed controls.

Serum samples were taken before and after operation (days 1, 4, 30, 150) from patients undergoing hepatic resection ($n = 16$) and liver transplantation ($n = 12$), and from patients in three control groups· major abdominal surgery ($n = 7$), renal transplantation ($n = 9$) and normal volunteers ($n = 20$). The human colonic cancer cell line LoVo was incubated for 4 days in a 5 per cent concentration of the patient's serum in a medium ($n = 5$ replicates). Tumour cell proliferation was measured by tritiated thymidine incorporation (TTI), expressed as counts per minute (c.p.m.). An enzyme-linked immunosorbent assay was used to measure HGF, expressed as optical density (OD). The immunosuppressed and non-suppressed control groups showed no significant differences from normal volunteers· median TTI 5557 c.p.m. median HGF 700 OD The *Table* shows median results for the test groups.

	Preop.	Day 1	Day 4	Day 30	Day 150
TTI (c.p.m.)					
Resection	11025	11190*	9509	8513	11158
Transplant	2124	3311	2582	2173	—
HGF (OD)					
Resection	1200*	1895†	1980*	1915*	1350*
Transplant	1415*	1850*	980	815	—

*$P < 0{\cdot}05$ *versus* control (Mann–Whitney *U* test)

Serum from patients having liver resection had high levels of HGF and stimulated tumour cell growth throughout the experiment. Liver transplant recipients had high levels of HGF before and immediately after surgery, with rapid resolution, and did not stimulate tumour cell line growth. Activation of HGF receptors on colorectal tumour cells is unlikely to be the cause of any systemic response enhancing tumour regrowth.

Laparoscopic surgery reduces postoperative adhesions by increasing peritoneal fibrinolysis

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Minimal access surgery has the potential advantage of reducing postoperative adhesion formation and resultant morbidity. This study investigated the effect of resectional laparoscopic surgery on peritoneal fibrinolysis and adhesion formation in a rodent caecal ligation model.

Male WAG rats were divided to three groups: controls ($n = 6$), open ($n = 16$) and laparoscopic ($n = 16$) surgery Open caecal ligation consisted of a 5-cm midline incision followed by ligation of the terminal 2 cm of the caecum. Laparoscopic surgery was achieved through two 5-cm ports, with intracorporeal mobilization and extracorporeal caecal ligation as in the open group. Pneumoperitoneum was maintained throughout the procedure. At 4 days and 3 weeks rats were killed Adhesion scores were taken and abdominal wall samples obtained for plasminogen activator activity (PAA), which was measured using the fibrin plate technique.

	Baseline controls	4 days open	4 days laparo-scopic	3 weeks open	3 weeks laparo-scopic
PAA (units cm^{-2}) × 10^2	14·5(3·2)	19·2(2·5)	24·5(8·0)	12·5(1·3)	450(20·0)†
Adhesion score	None	None	None	19·33(6·8)*	5·33(1·94)

Values are mean(s.d.) *$P < 0{\cdot}0001$ (open *versus* Mann–Whitney *U* test), †($P < 0{\cdot}001$ (3 weeks laparoscopic *versus* 3 weeks open and control, Kruskal–Wallis analysis of variance)

There was no significant change in fibrinolytic activity at 4 days in both surgery groups compared with baseline controls. However, at 3 weeks, PAA was significantly higher in the laparoscopic group compared with both the open and control groups. This rise was associated with a marked decrease in both the number and severity of adhesions found in the laparoscopic group. In conclusion, laparoscopic surgery results in a significant increase in peritoneal fibrinolytic activity which may be responsible for the consequent reduction in adhesion formation.

Src-mediated activation of the human neurotensin–neuromedin N promoter

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The gene encoding neurotensin and neuromedin N (*NT/N*) is expressed in differentiated endocrine cells of the adult small bowel. The authors have previously identified the Ras pathway as important for *NT/N* expression. Src kinase, a non-receptor tyrosine kinase, interacts with Ras and has been implicated in growth and differentiation of various tissues The purpose of this study was to determine whether Src can activate the *NT/N* promoter

Methods CaCo-2 cells, a human colonic cancer line that can differentiate to a small bowel phenotype, were transiently transfected with human *NT/N* promoter constructs (5′ deletions or linker scanning mutations) linked to the luciferase reporter gene and either a Src expression vector (pMvSrc) or the empty vector (pEVX). To control for transfection efficiency, cotransfection with a β-galactosidase plasmid was performed. Cells were harvested 48 h later and analysed for luciferase and β-galactosidase activity.

Results Cotransfection of the Src expression vector resulted in a fourfold to eightfold increase in *NT/N* promoter induction. Using sequential 10 bp linker scanning mutations of the *NT/N* promoter, loss of Src-mediated induction with mutation of a proximal activating protein (AP) 1–adenosine 3′, 5′-cyclic monophosphate (cAMP) responsive element (CRE) site located between −50 to −41 was demonstrated.

Conclusion Src increases *NT/N* promoter activity in the gut-derived CaCo-2 cell line possibly acting, in part, through a number of cells was scored for each tumour on a scale of less than or more than 50 per cent (tumour cells expressing signal).

	VEGF expression		FLT-1 expression		
	≤50%	≥50%	≤50%	≥50%	Total
Invasive ductal carcinoma	8	32	5	35	40
Invasive lobular carcinoma	4	4	1	7	8
Bone metastases	2	9	1	10	11

VEGF messenger RNA (mRNA) was expressed by 11 per cent of malignant epithelial cells and, surprisingly, 87·5 per cent of these cells also expressed mRNA for FLT-1. In bone metastases, both VEGF and FLT-1 were expressed by all the metastatic tumour cells and also by osteoblasts (in four biopsies normal bone was present), and this indicates a potential relationship between angiogenesis and formation of new bone.

These data suggest that VEGF, acting via FKT-1 to a possible autocrine pathway, may potentiate the development of bone metastases.

Infusion of basic fibroblast growth factor increases hepatic tumour vascularity and blood flow

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Chemotherapy uptake by colorectal liver metastases is limited by hypovascularity. Interstitial basic fibroblast growth factor (bFGF) infusion increases tumour vascularity and blood flow in subcutaneous tumours. An attempt was made to increase liver metastasis vascularity and blood flow by hepatic arterial bFGF infusion.

Chester Beatty Hooded rats bearing hepatic Hooded Sarcoma-N tumours were infused with either bFGF (5μg per day) or saline for 7 days, via the gastroduodenal artery using an osmotic minipump. After a short infusion of the blood flow tracer [^{125}I]iodoantipyrine (^{125}I-IAP), the liver was excised and frozen in liquid nitrogen. Liver and tumour blocks were sectioned for autoradiographic and immunohistochemical analysis. Blood vessels were stained using the antiendothelial antibody MCA-048, and vascular volume and vessel count were determined at ×400 magnification using microscopic graticule counting. Blood flow was measured by quantitative autoradiography. Some 25 tumours in ten rats were analysed.

	Saline ($n = 11$)	bFGF ($n = 14$)	P*
Vessel volume (%)	1·1 (0·7–3·3)	2·9 (1·4–6·4)	0·03
Vessel count (mm^{-2})	583 (466–1701)	2041 (630–3122)	0·07
^{125}I-IAP T:N ratio (mm from tumour edge)			
1	0·46 (0·2–0·8)	0·38 (0·2–0·6)	n.s.
2	0·15 (0–0·6)	0·35 (0–0·5)	<0·01
3	0·15 (0–0·8)	0·37 (0–0·9)	<0·01

Values are median (interquartile range). *Mann–Whitney *U* test

It is concluded that a 7-day hepatic arterial bFGF infusion increases both metastasis vascularity and central tumour T:N blood flow ratio.

Differential role of monocytes and natural killer cells in mediating antibody-dependent cell-mediated cytotoxicity of colorectal tumour cells

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The therapeutic use of murine monoclonal antibodies is associated with human anti-mouse antibody. To circumvent this, humanized (chimeric) antibodies have been developed. The ability of monocytes and natural killer (NK) cells to lyse colorectal tumour cells in an antibody-dependent cell-mediated cytotoxicity assay was investigated.

Peripheral blood mononuclear cells (PBMCs) were isolated from seven patients with colorectal cancer and from nine normal donors. Four effector cell populations were derived: PBMC, monocyte depleted, NK cell depleted, monocyte and NK cell (double) depleted. Magnetic beads coated with antibody (CD14 for monocytes, CD56 for NK cells) were used for cell depletion. An 18-h ADCC assay lysis. Murine antibodies (m17-1A, m323A3), chimeric antibodies (c17-1A, c323A3, cSF25) and an irrelevant antibody control were compared.

The overall median percentage lysis was significantly higher in the patient group ($P = 0·04$). A significant reduction in lysis was noted in both the monocyte-depleted populations with m17-1A and m323A3 ($P = 0·02$). With cSF25 there was a significant reduction in percentage specific lysis in both patient and control monocyte-depleted and NK cell-depleted populations ($P = 0·3$). With cSF25 and c323A3 there remained a significant level of killing in the double-depleted cell populations ($P = 0·23$ and $P = 0·19$ respectively) in both patients and controls.

This demonstrates that both monocytes and NK cells are important for tumour cell lysis. However, murine antibodies mediate tumour lysis via monocytes, whilst humanized antibodies recruit both monocytes and NK cells. Chimeric antibodies may also mediate killing by other pathways unavailable with murine antibodies.

REG gene transcripts in normal-appearing colorectal mucosa are commoner near to tumours

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Expression of the *REG* gene in colorectal cancer is associated with poor prognosis in the 55 per cent of tumours in which it is detectable. Expression is less common in normal-appearing colonic mucosa sampled from the same resected specimens as tumour tissue. In this study the pattern of *REG* expression was investigated in normal-appearing colonic mucosa sampled at set distances from the tumour and from the furthest resection margin.

Fresh samples of tissue were obtained from 23 surgical specimens resected from patients with colorectal cancer. Mucosa was sampled from the furthest resection margin from the tumour, at sites 4 and 2 cm from the tumour edge, and from the tumour itself. Reverse transcriptase–polymerase chain reaction was carried out using primers to identify *REG* gene transcripts, and the colonic cancer cell line SW948 was used as a positive control for expression.

	Carcinoma	2 cm	4 cm	6 cm	Distal margin
REG-expressing samples	13*	12†	7	4	4

*$P = 0·02$ (carcinoma *versus* distal margin and 6 cm); †$P = 0·03$ (2 cm *versus* distal margin and 6 cm) (χ^2 test with Yates' correction)

collagen. Heterotypic cell binding was assessed on adherent interferon σ activated peritoneal macrophages

	Control	Helium	Carbon dioxide	*P*
Homotypic binding ratio	1·6(0·8)	1·5(0·9)	1·1(1·3)	<0·05*
Cell detachment (nm)	0·65(0·14)	0·63(0·12)	0·38(0·08)	<0·01†
Fibronectin adhesion (%)	51(6·8)	38(6·1)	5·5(1·5)	<0·001†
Collagen IV adhesion (%)	64(9·7)	47(7·9)	21(4·3)	<0·001†
Peritoneal macrophage binding (%)	59(6·9)	53(6·3)	20(6·9)	<0·001†

Values are mean(s.d.) Kruskal–Wallis analysis of variance (ANOVA), †one-way ANOVA

Conclusion This study demonstrates that carbon dioxide pneumoperitoneum may directly and specifically influence the metastatic cascade by inducing functional changes in tumour cells, resulting in reduced cell–cell adhesion, promotion of cell detachment and impairment of cancer cell binding to immune effector cells.

P53 immunohistochemistry identifies 'at risk' patients with Barrett's oesophagus

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Introduction Screening for patients with Barrett's oesophagus requires the identification of a 'dysplastic' subgroup at risk from malignant progression. However, the histopathological boundary definition between metaplasia and low-grade dysplasia is difficult. Accumulation of aberrant p53 protein is associated with progression through grades of dysplasia to adenocarcinoma of the oesophagus.

The aim of this study was to assess the value of immunohistochemistry for p53 protein, as an adjunct to haematoxylin and eosin staining for the identification of patients with dysplasia.

Methods Representative paraffin sections from 104 patients with histological metaplasia ($n=48$), low-grade dysplasia ($n=7$) or carcinoma ($n=49$) were microwaved to retrieve the p53 antigen. Immunohistochemical identification of p53 was determined using murine Do-7 monoclonal antibody with the streptavidin–biotin detection system. A diagnosis based on p53 staining intensity and distribution was established and compared with the original histological diagnosis. Where a discrepancy existed between these independent diagnoses, the original haematoxylin and eosin-stained slides were re-examined.

Results Forty-five of 49 adenocarcinomas stained positively for p53 protein. The results for p53 staining in non-malignant Barrett's were as follows:

	p53 diagnosis	
Histological diagnosis	Metaplasia	Low-grade dysplasia
Metaplasia	38	10
Low-grade dysplasia	2	5

There was 88 per cent concordance in the diagnoses between the two methodologies. Ten samples with metaplasia on haematoxylin and eosin staining were reassigned as being low-grade dysplasia on p53 staining criteria. When the corresponding haematoxylin and eosin-stained sections were reviewed, five of the ten were rediagnosed as low-grade dysplasia.

Conclusion P53 immunohistochemistry can identify additional patients with low-grade dysplasia on routine haematoxylin and eosin staining, who warrant surveillance endoscopy.

Colonic tumour cells show a reduced capacity for the oxidative metabolism of butyrate

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Butyrate provides up to 70 per cent of the energy needs of colonocytes and is a major stimulator of colonic mucosal growth, regulating specific genes. In culture, colonic cancer cells stop growing in the presence of butyrate and begin to differentiate, in contrast to normal cells which grow more rapidly.

The aim of this study was to compare the oxidative metabolism of butyrate and two other substrates, glucose and glutamine, in human cancer and normal mucosa.

Biopsy specimens (5–15 mg) of normal and tumour tissue were obtained from 31 patients undergoing right hemicolectomy. Each specimen was assayed in duplicate for the conversion of each fuel to [^{14}C]carbon dioxide in media containing all three fuels.

	Substrate oxidation (nmol mg wet wt^{-1} h^{-1})*		
Tissue	Glucose (10 mmol l^{-1})	Glutamine (5 mmol l^{-1})	Butyrate (5 mmol l^{-1})
Mucosa	0·33 (0·28–0·38) ($n=30$)	1·5 (1·0–2·2) ($n=18$)	18·3 (15·7–22·4) ($n=31$)
Tumour	0·34 (0·25–0·49) ($n=31$)	1·1 (0·6–2·0) ($n=18$)	5·1 (4·0–7·2) ($n=31$)

*Values are median (95 per cent confidence interval) and number of patients

Butyrate catabolism was significantly lower in tumour than in normal mucosa ($P=0·001$, Wilcoxon test). There were no differences in the oxidation of glucose and glutamine. Adenosine 5′-triphosphate production from all three substrates in tumours was 33 per cent that in normal tissue, a reduction accounted for totally by diminished butyrate utilization.

These data show that butyrate has a significantly reduced role in oxidative metabolism in tumour cells compared with that in normal mucosa, and may explain the differences in their growth behaviour. Colonic cancer cells probably use an alternative fuel source, knowledge of which may affect therapy.

Bone metastases in breast cancer and association with vascular endothelial growth factor and its receptor

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Bone metastases are of significant importance in patients with advanced breast cancer. Over 70 per cent of these patients will develop bone metastases at some stage of their illness. The median survival is 24 months but approximately 10 per cent will be alive 5 years after the diagnosis of bone metastases. Recent evidence suggests that growth factors are important modulators of metastatic tumour growth. Vascular endothelial growth factor (VEGF), a specific mitogen for endothelial cells, is known to bind osteoblasts and regulate their differentiation. FLT-1, a transmembrane kinase receptor, represents a high-affinity receptor for VEGF. To determine the expression of VEGF hybridization with cDNA probes to both genes was performed. Reaction product was assessed using a system in which the

In the *in vitro* study 96-well plates coated with type IV collagen, gelatin, fibronectin or Matrigel were pretreated for 30 min at 37° with phosphate-buffered saline (PBS) or HA solution (0·4 per cent in PBS). Each well was then seeded with 1×10^4 CC531s colonic cancer cells and incubated for 1 h after which the seeding efficiency was measured spectrophotometrically.

In the *in vivo* study 22 WAG rats underwent caecal resection via a midline laparotomy and were randomized to receive HA solution of PBS. The peritoneal cavity was coated with 5 mls of either solution immediately on entry into the abdomen A suspension of 2×10^5 CC531 cells was then injected evenly into the peritoneal cavity, which was coated once again before closure of the abdominal incision. Autopsy was performed at 3 weeks and the extent of tumour growth and intestinal adhesion formation rated using a standardized scoring system

	Seeding efficiency (%)				Tumour score	Adhesion score
	Collagen IV	Gelatin	Fibronectin	Matrigel		
HA	30·7(6·6)	22·8(2·1)*	18·2(3·5)†	26·4(12·4)*	4·0(4·4)*	1·6(0·5)*
Control	29·5(13·9)	34·3(4·8)	29·6(13·2)	67·4(35·8)	17·5(7·8)	3·0(0·6)

Values are mean(s d) *$P < 0·01$, †$P < 0·05$ *versus* control (unpaired *t* test)

HA reduces the ability of cancer cells to adhere to major components of the ECM Furthermore precoating the peritoneal cavity with HA solution resulted in a significant reduction in intraperitoneal adhesion formation and tumour growth.

Tumour necrosis factor inhibition and trinitrobenzenesulphonic acid colitis

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Tumour necrosis factor (TNF) is a proinflammatory cytokine which has been implicated in the pathogenesis of inflammatory bowel disease. The aim of this study was to investigate the effect of anti-TNF treatment in hapten-induced colitis and thus clarify the role of TNF in the pathogenesis of this model. The TNF inhibitors used were pentoxyphylline (PTX), a xanthine derivative and transcriptional inhibitor of TNF synthesis, and the monoclonal anti-TNF antibody cTN3. cB0006, an idiotype control antibody, was used to control for non-specific immunoglobulin (Ig) G effects.

Under general anaesthesia 30 mg trinitrobenzenesulphonic acid (0·6 ml) and 50 per cent ethanol (0·25 ml) were instilled into the colon of male Wistar rats (250–300 g) to induce colitis, control animals received an equal volume of 0·6 per cent saline. Five groups ($n = 16$) were used: (1) controls; (2) untreated colitics, (3) colitics treated with cTN3 before induction of colitis; (4) colitics treated with cB0006 before induction of colitis; (5) colitics treated with PTX before and after induction of colitis. The effect of treatments on colonic macroscopic score (CMS), per cent change in body-weight (per cent CBW) and serum interleukin 6 (IL) concentration are shown below.

Group	CMS (0–10)	%CBW	IL-6
Control	0·13(0·1)	7·22(1·0)	0
Colitic	8·25(0·49)	− 10·8(3·8)	870(400)
cTN3	6·75(0·57)	− 5·8(3·4)*	39(39)*
cB0006	6·75(0·58)	− 9·2(4·1)	1226(984)
PTX	6·37(0·38)*	− 6·7(3·5)	132(53)*

Values are mean(s.e.m.) *$P < 0·05$ *versus* colitic (Mann–Whitney *U* test)

TNF is an important early mediator in the development of tumour necrosis factor acid is an important early mediator in the development of trinitrobenzenesulphonic colitis. The effect of cTN3 is not a non-specific IgG effect.

Cisplatin requires mut S homologue 2 for induction of apoptosis

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Hereditary non-polyposis colorectal cancer (HNPCC) is an inherited cancer syndrome accounting for 5 per cent of all colorectal cancers. It is characterized by early onset, right-sided colorectal cancers with defective DNA mismatch repair. Some 70 per cent of patients carry germline mutations in the DNA mismatch repair enzyme mut S homologue 2 (MSH2). Little is known about the responsiveness of this group of tumours to chemotherapy. The aim of this study was to determine whether DNA damage induced by cisplatin can couple to apoptosis through an MSH2-dependent pathway.

Wild-type and transgenic mice with a homozygous deletion in the MSH2 gene were injected with cisplatin 10 mg kg^{-1} intraperitoneally. The small intestine was harvested and fixed at various time points, and apoptosis was scored by light microscopy. The *Table* shows the prevalence of apoptosis in 50 small intestinal crypts

	0 h	3 h	6 h*	12 h*	24 h*
Wild-type	3·7	64·7	185·7	158·3	109·3
Homozygotes ($MSH^{-/-}$)	2·3	21·3	126·3	130·7	81·0

Values are mean ($n = 3$). $P < 0·05$, *statistically significant

Cisplatin mediates apoptosis through an MSH2-dependent pathway in the murine small intestine. Thus HNPCC tumours which lack MSH2 are likely to respond poorly to chemotherapeutic agents such as cisplatin and alkylating agents that require MSH2 for recognition of the DNA damage.

Intraoperative modulation of the metastatic cascade by carbon dioxide pneumoperitoneum

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Introduction Tumour metastasis is a complex phenomenon that involves several sequential steps: loss of cell–cell adhesion, increased cell substrate detachment, evasion of cytotoxic immune cells, and finally implantation and growth at a distant site. Previous work has demonstrated that exposure of cancer cells to carbon dioxide pneumoperitoneum results in increased metastatic potential. Factors that might be responsible for this process *in vitro* were examined.

Methods Colonic cancer CC531s cells were incubated at 37°C in control conditions (95 per cent air, 5 per cent carbon dioxide), 100 per cent carbon dioxide or 100 per cent helium at 15 mmHg for 3 h. Homotypic cell adhesion was measured by assessment of the conjugate frequency of cells in suspension immobilized in agarose. Cell substrate detachment was assessed in tumour monolayers by the enzymatic detachment assay and by measuring postincubation substrate adhesion to fibronectin and type IV transplantation, and appears to have a comparable side-effect profile to the new formulation of cyclosporin (Neoral).

Deuterium oxide–University of Wisconsin solution improves vascular preservation

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The quality of preservation is vital for the outcome of organ transplantation Most research has focused on the beneficial effects of solvents rather than the solute itself An assessment was made of the alternative approach of altering the solute by proportionate replacement of water (H_2O) with deuterium oxide (D_2O), a non-radioactive isotope of water.

Rat thoracic aortic rings were allocated randomly to controls and University of Wisconsin solution (UW) based on 100 per cent H_2O (H100), 25, 50 or 100 per cent D_2O (D25, D50, D100). After 24, 48 or 72 h storage at 4°C viability was assessed by measuring contraction and relaxation of the rings in an organ bath after stimulation with phenylephrine and acetylcholine.

Results are expressed as the percentage in comparison with the control (100 per cent)·

	Group			
	H100	D25	D50	D100
Contraction (%)				
24 h	77*	81*	76*	75*
48 h	58*	75*†	61*	53*
72 h	54*	69*†	51*	33*†
Relaxation (%)				
24 h	95	110†	110†	109†
48 h	71*	97†	96†	84*†
72 h	57*	89†	63*	58*

$^*P<0{\cdot}05$ *versus* control; $^\dagger P<0{\cdot}05$ D_2O group *versus* H_2O group (analysis of variance)

These results show that 25 per cent D_2O-based UW significantly improves both contractile and relaxant response for up to 72 h compared with the generally used H_2O-based equivalent This might have implications for clinical organ transplantation.

Iron deficiency enhances cholesterol gallstone formation

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Cholesterol gallstones occur most commonly in multiparous women but the causes of this phenomenon remain unclear. This same patient population is also prone to chronic iron deficiency anaemia. In addition, iron is known to play an important role in hepatic enzyme metabolism. Therefore, the hypothesis that iron deficiency would alter hepatic cholesterol metabolism and enhance cholesterol gallstone formation was tested

Forty adult prairie dogs were fed either a control iron-supplemented (200 parts per million (p.p m.)), an iron-deficient (Fe $-$) (8 p.p.m.), a 0 4 per cent cholesterol iron-supplemented (Xol) or a 0·4 per cent cholesterol iron-deficient (Xol + Fe$^-$) diet After 8 weeks, gallbladder and hepatic bile, serum and liver were harvested. Gallbladder bile was examined for gallstones, and the number of crystals per high-power field was counted. Levels of bile cholesterol, phospholipids and bile acids were measured, and a cholesterol saturation index (CSI) was calculated Mean(s.d.) values for gallbladder bile are shown in the *Table*.

		Xol crystals			
Group	*n*	Animals (%)	No per hpf	Xol (mole %)	CSI
Control	10	20	5(3)	2·3(0·3)	0·67(0 08)
Fe$^-$	10	80*	7(3)	2·7(0·2)	0·75(0·06)
Xol	10	100*	49(9)*†	4·5(0 5)*†	0·93(0·06)*
Xol + Fe$^-$	10	100*	79(10)*†‡	6·0(0·4)*†§	1 27(0·1)*†§

$^*P<0{\cdot}05$ *versus* control, $^\dagger P<0{\cdot}05$ *versus* Fe$^-$, $^\ddagger P=0{\cdot}06$ *versus* Xol, $^\S P<0{\cdot}05$ *versus* Xol (analysis of variance)

These data suggest that an iron-deficient diet: (1) increases gallbladder bile cholesterol and CSI, and (2) promotes cholesterol crystal formation. It is concluded that iron deficiency plays a previously unrecognized role in the pathogenesis of cholesterol gallstone formation in women.

α-Tricalcium phosphate as a drug carrier for targeting chemotherapy in rats bearing abdominal carcinomatosis

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α-Tricalcium phosphate (α-TCP) particles were evaluated as a drug carrier in rats bearing abdominal carcinomatosis. α-TCP is biomaterial and its chemical properties are similar to those of hydroxyapatite; the particles measure 50–150 μm in size and have numerous open micropores 1–3 μm in diameter, which offer adequate space for incorporating with drugs. The slow-releasing drug, α-TCP–carboplatin (CBDCA), was made and the following were studied: (1) *in vitro* release of CBDCA from α-TCP–CBDCA in albumin solution; (2) localization and biodegradation of α-TCP particles in the abdominal cavity of Donryu rats; (3) distribution of CBDCA from α-TCP–CBDCA administered intraperitoneally in serum, ascites and various organs; and (4) the pharmacokinetics of α-TCP–CBDCA in rats with AH-130 abdominal carcinomatosis.

The following results were observed: (1) 60 per cent of CBDCA was dissolved in 1 week; the rest of the drug was suggested to come out very slowly. (2) α-TCP particles were especially taken up in the milky spot and stomata in 1 week, and dissolved gradually in 6 months without side-effects. (3) The CBDCA concentration in ascites and the greater omentum were higher in the α-TCP–CBDCA intraperitoneal group than in CBDCA intraperitoneal and intravenous groups. (4) Administration of α-TCP–CBDCA intraperitoneally was effective in prolongation of survival of rats with AH-130. These results suggest that the efficacy of CBDCA may be enhanced by utilizing α-TCP particles as a drug carrier.

Hyaluronate alters cell matrix adhesion *in vitro* and reduces postoperative tumour growth

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Intraperitoneal administration of various agents has been used in an attempt to prevent interaction between cancer cells and extracellular matrix (ECM) but with limited success. CD44 is a broadly distributed cell adhesion molecule which is important for cell–cell and cell–substrate interactions and has been implicated in the spread of epithelial cancer. The main ligand for CD44 is hyaluronate (HA), and coating the peritoneum with hyaluronate has been employed clinically to prevent postsurgical abdominal adhesions. The aim of this study was to investigate the effect of HA on cancer cell interaction with ECM proteins *in vitro*, and on tumour growth and intra-peritoneal adhesion formation *in vivo* using a CD44-positive cell line.

application of this technique has been limited by the toxicity of lethal conditioning, which is believed to be necessary to achieve bone marrow stem cell engraftment in major histocompatibility complex (MHC)-disparate donor–recipient combinations. The authors previously reported that transplantation of MHC-disparate bone marrow into recipients conditioned with a single dose of antilymphocyte globulin (ALG) on day −3 followed by 300 cGy TBI on day 0 and 200 mg kg^{-1} cyclophosphamide (CyP) on day +2 results in stable mixed chimerism and donor-specific tolerance for solid organ grafts. ALG is a polyclonal serum that binds to natural killer (NK) cells as well as to CD4$^+$ and CD8$^+$ cells. The focus of the present study has been to define, by substituting monoclonal antibodies (mAbs) for the ALG, what populations in the host microenvironment are targeted by ALG pretreatment of the recipient.

C57BL/10SnJ (H2^b) mice were pretreated intravenously with 50 μl anti-CD4 (TIB207) and 100 μl anti-CD8 (TIB105) days −3 and −1. Successful depletion was documented by flow cytometry of peripheral blood lymphocytes. The animals were irradiated with 300 cGy and transplanted with 15×10^6 B10.BR/SgSnJ (H2^k, $n = 4$) of BALB/c (H2^d, $n = 3$) bone marrow cells, followed by 200 mg kg^{-1} CyP intraperitoneally on day +2. Without ALG pretreatment historically only 20 per cent of animals engrafted, compared with 71 per cent of anti-CD4 and CD8 pretreated animals. This is similar to the increased engraftment seen with ALG pretreatment. In addition, the level of chimerism was highest in animals with mAbs.

	Engrafted animals (%)	Level of engraftment (%)*
No pretreatment ($n = 5$)	20	22(0)
ALG pretreatment ($n = 12$)	83	30(7·4)
CD4/CD8 pretreatment ($n = 7$)	71	53(0·1)

Values are mean(s.d.)

It is concluded that CD4$^+$ and/or CD8$^+$ cells in the recipient's haematopoietic environment play an important role in resistance to engraftment of allogeneic bone marrow. It appears from these data that CD4$^+$ and/or CD8$^+$ cells, rather than NK cells, are the population(s) that block allogeneic engraftment and are removed by ALG. As mechanisms of engraftment are better understood, specific targeting of recipient cell populations will be possible.

Nitric oxide activity in cirrhotic patients undergoing liver transplantation

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Increased expression of nitric oxide (NO) has been implicated in the systemic and splanchnic hyperdynamic circulation of decompensated liver cirrhosis, but the precise role of NO in the pathogenesis of portal hypertension associated with cirrhosis remains unclear

The total concentrations of nitrite plus nitrate (NOx) in the systemic and portal venous blood and the activities of constitutive NO synthase (cNOS) and inducible NO synthase (iNOS) in the liver and omentum of patients with decompensated cirrhosis and portal hypertension undergoing orthotopic liver transplantation ($n = 9$) and in non-cirrhotic patients undergoing liver resection (controls, n7) were measured. Institutional ethical committee approval was obtained for the study.

Systemic venous concentrations of NOx were similar in cirrhotic and control patients (mean(s.e.m.) 22·34(9·90) *versus* 27·64(8·74) μmol l^{-1}, $P = 0{\cdot}69$). In contrast, portal venous concentrations of NOx were significantly higher in patients with cirrhosis than in controls (49·30(9·99) *versus* 15·47(1 52) μmol l^{-1}, $P = 0{\cdot}008$). cNOS activity was significantly lower in cirrhosis than in controls in both the liver (4·43(0·49) *versus* 5·99(0·47) pmol g^{-1} min^{-1}, $P = 0{\cdot}04$) and the omentum (0·82(0·23) *versus* 2·02(0·32) pmol g^{-1}min^{-1}, $P = 0{\cdot}01$). However, iNOS activities were similar in cirrhosis and control groups in both liver (4·21(0·72) *versus* 5·46(0·81) pmol g^{-1} min^{-1}, $P = 0{\cdot}26$) and omentum (1·41(0·12) *versus* 1·72(0·10) pmol g^{-1}min^{-1}, *versus* $P = 0{\cdot}07$).

The authors speculate that decreased hepatic cNOS activity, with consequently reduced NO release into the microvascular bed, may contribute to increased intrahepatic portal vascular resistance in patients with cirrhosis. Enhanced portal venous NOx concentration indicates increased splanchnic NO release. The anatomical site of increased NO synthesis, however, remains to be established. These data indicate the need for further research into differential expression of cNOS and iNOS in the splanchnic organs, which might lead to the development of novel therapeutic agents in the management of portal hypertension

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Prospective randomized study of tacrolimus (Prograf) *versus* cyclosporin (Neoral) as primary therapy in 80 consecutive adult cadaveric renal transplants

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The role of primary immunosuppression with tacrolimus is well established in hepatic transplantation; however, its role in renal transplantation is less well defined and requires further evaluation.

In an ongoing study, 80 patients transplanted in 1996 received tacrolimus (Prograf) or cyclosporin (Neoral) as primary immunosuppression in a triple-therapy regimen. Tacrolimus was commenced at 0·2 mg kg^{-1} day^{-1} and cyclosporin at 8 mg kg^{-1} day^{-1}; both drugs were administered in two divided doses and adjusted according to clinical response and 12-h trough blood levels. At the end of the second week the median dose of tacrolimus was 0·15 mg kg^{-1} day^{-1} (median trough 9·6 ng ml^{-1}) and that of cyclosporin was 6·3 mg kg^{-1} day^{-1} (median trough 191 ng ml^{-1}).

	Tacrolimus ($n = 40$)	Cyclosporin ($n = 40$)
Delayed function requiring dialysis	5	7
Median creatinine level at 3 months (μmol l^{-1})	128	135
Rejection		
No. of patients	16	13
No. of episodes	26	22
Graft loss (including death)	0	6*
Cytomegalovirus infection	0	4
New cases of diabetes mellitus	3	2
Median cholesterol level at 3 months (mmol l^{-1})	5·6	6·6
Antihypertensive index	1·90	1·95

*$P < 0{\cdot}02$ (χ^2 test)

At follow-up of 3 months, 39 of 40 patients are still receiving tacrolimus, one having converted to cyclosporin because of tacrolimus enteropathy. Five patients in the cyclosporin group were converted to tacrolimus owing to refractory rejection, with satisfactory outcome in four and one graft failure.

It is concluded that tacrolimus at the starting dose of 0·2 kg^{-1} day^{-1} and with trough levels lower than previously recommended represents an effective and safe therapy as a primary immunosuppressive agent following cadaveric renal

Pulmonary venous oxygen tension in the allograft lung was worst in group 2 ($P<0\cdot001$). Group 1 was better ($P<0\cdot001$), but groups 3 and 4 were superior to all other groups ($P<0\cdot001$). Pulmonary vascular resistance was also greatest in group 2, lower in group 1, but lowest in groups 3 and 4.

There were no differences in any of the outcome measured between groups 3 and 4.

It is concluded that low pressure reperfusion modulates reperfusion injury. The addition of a period of leucocyte depletion of InSP6 in the recipient confers significant additional benefit, but no differences between these interventions in terms of their effectiveness could be demonstrated

Does allogeneic vascularized bone marrow transplantation prolong allogeneic free skin graft survival: the possible role of microchimerism

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It is known from recent reports that the survival time of human allografts may be prolonged in recipients of donor-type bone marrow cells (BMCs). The microchimerism is suggested to be responsible for partial tolerance to donor major histocompatibility complex (MHC) antigens. There are also opposing reports of lack of correlation between microchimerism and tolerance. The authors have noticed that bone marrow transplanted in a vascularized limb graft providing a continuous supply of donor BMCs may prolong the survival time of skin from the same donor. Skin is a strongly immunogeneic tissue and grafted to an allogeneic recipient, requires high doses of immunosuppressive drugs to prevent rejection. The immunological enhancement and donor-specific transfusion are most effective in allogenic skin rejection. The question arises whether microchimerism plays a role in the prolonged survival of skin allografts. The aim of this study was to follow the kinetics of microchimerism after allogeneic vascularized bone marrow transplantation (VBMT) and the rejection process in skin transplants

Methods BN (RT1n) rats served as donors and LEW (RT1l) rats as recipients of VBMT Hind limb was transplanted, followed by a full-thickness skin graft on the dorsum. Grafts were scored daily for the degree of rejection, which was considered complete when non-viable residual could be seen. Microchimerism was followed with two methods. Blood, spleen, mesenteric lymph nodes (MLNs) and bone marrow (BM) cells were stained with monoclonal antibody OX27 directed against MHC class I polymorphic RT1 on BN cells In the other method, sex-determining regions of the Y chromosome were used as primers to determine the presence of DNA from the donor. Studies were carried out in groups· group 1, allogeneic limb and a free skin flap transplanted simultaneously; group 2, allogeneic free skin flap. In both groups CSA (17 $\text{mg kg body-weight}^{-1}$) was given to the recipient for 30 days. Observations were continued for a further 70 days without CSA. Control animals did not receive CSA. Immunohistochemical staining of graft biopsies, FACS and polymerase chain reaction analysis of chimeric cells were performed

Results Allogeneic free skin grafts were rejected 6–7 days after weaning from CSA In the group with VBMT of free flap skin, grafts survival was prolonged by a factor of two or three after cessation of CSA therapy. BN cells were found in LEW blood in at a mean(s d.) of 3·3(5·2) per cent, spleen 2·02(2·7 per cent, MLNs 0·7(1·4) per cent, BM 0·4(0·7) per cent and BN VBMT 1·5(2·5 per cent).

Conclusion Free skin allografts in rats treated with CSA always revealed signs of chronic rejection and were rejected totally after discontinuation of CSA therapy. BM cells from VBMT significantly prolong free flap survival after weaning of CSA Free skin allogeneic grafts enjoy prolonged survival after weaning from in rats with transplanted vascularized BM from the same donor. Donor-derived cells and DNA can be detected in recipients The continuous supply of donor BM cells may produce a stable microchimerism, presumably responsible for facilitation of skin grafting.

In situ warm ischaemia of rat kidney with contralateral nephrectomy: phosphate-buffered sucrose is protective

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The protective role of preservation fluid in the prevention of the harmful effects of warm ischaemia and reperfusion in a rat model is reported.

Male Wistar rats (300–350 g) were anaesthetized by intraperitoneal injection of inactin (120 mg kg^{-1}). An intravenous infusion was set up at 6 ml h^{-1} sodium chloride 125 mmol l^{-1}, bicarbonate 25 mmol l^{-1}, also containing 37 MBq l^{-1} [^{3}H]inulin (for inulin clearance). A laparotomy was performed and both ureters were cannulated for serial urine collection. An equilibration period of 1 h was allowed after surgery, after which urine was collected for 1 h (control). Blood supply to the left kidney was then isolated and the kidney was either not flushed or flushed with 0·5 ml 0·9 per cent saline or phosphate-buffered sucrose (PBS140) at 37°. A clamp was then applied to left renal pedicle. After 45 min the clamp was released and a right nephrectomy was performed. Urine flow and composition from the left kidney were observed for further 4 h.

In the group where kidneys were not flushed before ischaemia ($n=7$), two rats died following reperfusion; the remaining five displayed marked reduction of inulin clearance and near isosthenuria. In the PBS140-flushed group ($n=7$), all rats survived with well maintained inulin clearance accompanied by a raised flow rate of relatively concentrated urine.

	Urine flow rate ($\mu\text{l min}^{-1}$)		Inulin clearance ($\mu\text{l min}^{-1}$)		Urine osmolality (mosm l^{-1})	
	Saline	PBS140	Saline	PBS140	Saline	PBS140
Pre-ischaemia	7·1(0·6)	7·8(1)	611(64)	721(108)	1078(53)	1153(183)
1 h post-ischaemia	2·5(1·0)	63·5(22)*	40(12)	504(87)†	442(31)	426(35)
2 h post-ischaemia	11·5(5·3)	36·3(11)*	39(21)	366(74)†	320(2)	464(34)†
3 h post-ischaemia	10·1(4·7)	26·1(9)*	31(14)	365(87)†	331(8)	499(37)†
4 h post-ischaemia	6·4(3·5)	12·9(2)*	14(6)	176(26)†	335(13)	552(54)†

Values are mean(s.d.). *$P=0\cdot004$ *versus* saline (cumulative for 4 h (*t* test), †$P\leq0\cdot01$ *versus* saline (*t* test)

PBS140 provided effective protection to the rat kidney against damage caused by warm ischaemia and reperfusion. This model provides a useful tool in the evaluation of renal preservation fluids.

Chimerism with partial recipient conditioning: targeting of CD4$^+$ and CD8$^+$ cells in the recipient marrow space permits chimerism with reduced conditioning

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It has been demonstrated in rodent models as well as in primates, including humans, that tolerance for solid organ transplantation can be achieved by bone marrow chimerism. Even chronic rejection appears to be prevented.[1] The clinical

Samples were obtained from the left mammary artery (IMA), the saphenous vein (VSM) and the right atrial appendage (RAA) before the start of extracorporeal circulation. The specimens were frozen immediately in liquid nitrogen and subsequently analysed for NA high-performance liquid chromatography (HPLC with electrochemical detection), ATII and ET radioimmunoassay, nucleotides adenosine 5′-triphosphate (ATP), adenosine 5′-diphosphate, adenosine 5′-monophosphate (AMP), guanosine 5′-triphosphate, guanosine 5′-diphosphate, nicotinamide adenine dinucleotide, nucleosides (adenosine, inosine) and nucleobases (hypoxanthin, xanthin) (HPLC with ultraviolet light detection). The tissue content was expressed per gram wet weight.

Results The mean(s d.) NA content of the examined tissues was (in nmol g − 1)· RAA 4·2(2·5), VSM 0·65(0·32) and IMA 0·38(0 22). The ATII levels were highest in IMA (median 630 pg/g) and VSM (370 pg/g) and lowest in RAA (94 pg g) The highest ET content (expressed in pg g) was found in IMA (median 3021) compared with VSM (831) and RAA (777). The ATP content of the vessels was barely detectable. The highest levels of AMP were found in RAA (0·39(0·001) μmol g^{-1} and the lowest in VSM (0·05(0·03). The adenosine content (in μmol l g^{-1} of RAA (0·44(0·11) was higher than that of IMA (0·37(0 09) and VSM (0 24(0·01)). The nucleoside content correlated with the duration of ischaemia

Conclusion The present findings show that both IMA and VSM contain large amounts of growth factors, which may be important for the development of myocardial and vessel remodelling. Under standard surgical conditions, there was no ATP detectable after preparation of the vessels. Concomitantly, tissue levels of AMP and adenosine increased, indicating ischaemic injury, particularly of the VSM. These findings suggest that the loss of high-energy phosphates during preparation of the vessels may trigger a response to injury that is mediated by the release of growth factors from the vessel, and may play an important role in the pathogenesis of later coronary bypass occlusion

Is the epidermis the source of the angiogenic stimulus in the microangiopathy of chronic venous disease?

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Neovascularization of the dermis is present in the skin of patients with lipodermatosclerosis (LDS) secondary to chronic venous disease (CVD). The molecular angiogenic stimulus causing this is not known A study was made of the expression of angiogenic growth factors in the skin of patients with CVD who had never suffered ulceration.

Ethical committee approval was obtained for this study. Skin biopsies were obtained from patients undergoing surgery for venous disease of the lower limb. Patients included ten with LDS and ten with varicose veins and unaffected leg skin. Growth factor expression in skin unaffected by venous hypertension was confirmed using breast skin from surgical resections (eight patients). An indirect immunohistochemical technique was used.

Expression of transforming growth factor β and fibroblast growth factor in CVD skin paralleled that seen in normal skin. The platelet-derived growth factor (PDGF) BB isoform was moderately upregulated in the epidermis of skin exposed to venous insufficiency, whereas PDGF-AA demonstrated increased expression at the junction of the epidermis and dermis, particularly in LDS skin Vascular endothelial growth factor (VEGF) was strongly upregulated in the cytoplasm of keratinocytes in LDS ($n = 10$). It was also upregulated in specimens from patients with clinically unaffected skin.

VEGF is a powerful angiogenic growth factor. The presence of the neovascularization of CVD occurring adjacent to epidermis in which VEGF expression is greatly upregulated suggests that epidermally derived VEGF may be the angiogenic stimulus causing the cutaneous microangiopathy of CVD.

Preoperative induction with tacrolimus (Prograf) does not have a detrimental effect on primary graft function in adult cadaveric renal transplantation

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Delayed graft function is well known to have a detrimental effect on subsequent early and long-term results Administration of nephrotoxic drugs, such as cyclosporin or tacrolimus, before cadaveric renal transplantation has therefore been avoided.

Patients were randomized into two groups. tacrolimus induction (TI) and no tacrolimus before transplantation (NTI) groups. Tacrolimus was given orally at 0·1 mg kg^{-1}, which represents half the standard starting daily dose, at least 3 h before grafting. In addition 1 5 mg kg^{-1} azathioprine and 500 mg methylprednisolone were given to both groups. Each group also received 1 g kg^{-1} mannitol and 100 mg frusemide during operation, and a 24-h infusion of dopamine at 3 μg kg^{-1} min^{-1}.

All demographic data were comparable for both groups. No mechanical preservation was employed All grafts were stored in cold Marshall's solution before transplantation.

	TI group ($n = 40$)	NTI group ($n = 35$)
Total ischaemic time (h)	18·75	18·20
Median serum creatinine level preop. (μmol l^{-1})	857	844
Median serum creatinine level on postop. day 1 (μmol l^{-1})	590	629
Incidence of postop. dialysis	5 of 40	5 of 35

It is concluded that tacrolimus administered before operation at a dose of 0·1 mg^{-1} kg^{-1} has no adverse effect on primary graft function and resulted in a low incidence of delayed graft function

Inositol polyanions, pressure control and leucocyte depletion in lung reperfusion injury

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Leucocyte depletion, inositol polyanionic compounds and pressure control attenuate reperfusion injury but have not been compared directly. These interventions were investigated in a porcine model of left single-lung allotransplantation. Donor lungs were preserved with modified Euro-Collins solution for a mean ischaemic time of 18·6 h

Four groups of five animals each were investigated Group 1 was reperfused at a mean pulmonary artery pressure (PAP) of 25 mmHg, group 2 was reperfused at a mean PAP of 45 mmHg for 10 min before reducing the pressure to the same as that in group 1. Group 3 was reperfused at a mean pressure of 25 mmHg for 30 min with leucocyte-depleted blood from an extracorporeal circuit incorporating a Pall BC1-B filter. Group 4 was reperfused at 25 mmHg with the addition of intravenous inositol hexakisphosphate, an inhibitor of selectin-mediated neutrophil adhesion.

Leucocyte sequestration was observed in the first 10 min after reperfusion in groups 1 and 2, with maximal sequestration occurring at 2 min (group 1 pulmonary vein count 55 6 per cent of pulmonary artery count, group 2 43·9 per cent). Both leucocyte filtration and InSP6 abolished sequestration (PV count 95 3 per cent of PA count). Scheffé analysis of variance using summary measured showed that lung compliance was lowest in group 2. Low pressure reperfusion (group 2) significantly improved compliance ($P = 0{\cdot}002$), as did InSP6 and leucocyte filtration ($P < 0{\cdot}0001$).

At 60 min reperfusion	Sham I–R	I–R	HA + I–R
Rolling velocity (μm s^{-1})	45·12(1·16)	33·12(2·85)*	41·15(2·01)
No. adherent (per 100 μm)	4·60(1·20)	40·67(3·85)*†	12·20(0·88)
No. migrated (per field)	5·20(0·33)	53·17(9·46)*†	15·20(3·84)

Values are mean(s.e.m.). $^*P<0·05$ *versus* sham I–R, $^†P<0·05$ *versus* HA + I–R (analysis of variance with Scheffé *post hoc* test)

I–R significantly increased the number of adherent and migrated leucocytes at 30 and 60 min and reperfusion, and decreased the rolling velocity of leucocytes at 10, 30 and 60 min after reperfusion. Administration of HA significantly reduced leucocyte adherence and migration. It did not affect rolling velocity, which is mediated primarily by the selectin family of adhesion receptors. HA induced expression of HSP72 in lung, mesentery and gut These data indicate that pharmaceutical induction of HSP *in vivo* is possible and is associated with diminished leucocyte–endothelial interaction. This offers the opportunity to alter ischaemia–reperfusion-induced injury pharmaceutically.

Differential effects of neural and humoral response to brain death induction on cardiac function

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The hyperdynamic response following brain death due to an acute increase of intracranial tension has been well described in a large number of experimental studies. But the role of neural and humoral pathways during this reaction still remains unclear. The aim of this study was to characterize the different changes in cardiac function when brain death was mediated by neural or humoral pathways alone, or in combination.

Eighteen canine hearts were perfused parabiotically (perfusion pressure 80 mmHg) with a balloon placed in the left ventricle to estimate left ventricular contractility by pressure–volume relationships. The hearts were divided into three groups. In group 1, the heart was excised and perfused with blood from a support dog. Brain death was then induced by inflation of a subdural balloon in the support animal and the heart was exposed only to humorally mediated influences In group 2, the circulation of one animal was maintained by extracorporeal circulation and the heart was perfused parabiotically *in situ* with blood from a healthy support dog Brain death was then induced in the animal with the *in situ* isolated heart. In this setting the heart was affected only neurally In group 3, the heart was perfused parabiotically *in situ* with the animal's own blood, so that brain death induction led to a complete neurally and humorally mediated response. Heart rate, LV developed pressure (LVDP) and LV end-diastolic pressure were measured for 2 h after the induction of brain death. Myocardial coronary blood flow (CBF) and oxygen consumption ($M\dot{V}O_2$) were estimated.

Major changes in LV contractility were observed in the groups with humoral and neural plus humoral influences on the heart during the acute response, with maximum increases 5 min after induction of brain death in the humoral group (mean(s.d.) LVDP 175·2(11·6) *versus* 131·5(13·4) mmHg at baseline) and 3 min after brain death induction in the neural plus humoral group (LVDP 235·3(13·9) *versus* 132·8(8·9) mmHg at baseline). The reaction was significantly stronger with neural plus humoral pathways together ($P<0·05$) than with humoral pathways alone. CBF and ($M\dot{V}O_2$) increased significantly in both groups during the acute response. Neural influences alone resulted in a mild hyperdynamic response which started immediately, reached peak levels 20 s after brain death and returned to baseline values 3 min after brain death induction, with no significant changes in CBF or $M\dot{V}O_2$.

In conclusion, the response to brain death induction is triggered initially by an immediate increase in sympathetic activity, which leads to a marked systemic humorally mediated hyperdynamic response So the reaction is carried out at two different levels which produce maximum haemodynamic effects only in combination.

Monocyte CD14 expression and endotoxaemia in major aortic surgery: possible regulatory role of transforming growth factor β

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Background Monocyte CD14 and its soluble form sCD14 mediate the effects of endotoxin on monocytes and endothelium respectively. Transforming growth factor (TGF) β is known to inhibit this interaction The aim of this study was to measure the *in vivo* response of blood monocytes to endotoxaemia during major aortic surgery and the possible mediatory role of TGF-β during these procedures

Methods Some 24 patients undergoing elective types III and IV thoracoabdominal aortic aneurysm (TAAA) repair were studied. Blood was collected at incision, aortic clamping, reperfusion, and 1, 8 and 24 h after reperfusion Fresh samples were assayed for monocyte CD14 expression and plasma was assayed for endotoxin, sCD14, tumour necrosis factor (TNF) α and TGF-β_1

Results Although there was significant endotoxaemia during surgery in both groups of patients, peak plasma endotoxin levels were significantly higher in patients having TAAA repair ($P=0·001$). Levels of both monocyte CD14 and plasma sCD14 were significantly decreased in the TAAA group at reperfusion and 1 h postperfusion ($P<0·01$), whereas in patients having AAA repair a significant upregulation of CD14 was observed at 24 h postreperfusion ($P<0·01$), but no significant changes in sCD14 levels were observed. TNF-α concentration showed no significant changes during the study period in either group of patients. In the TAAA group, TGF-β_1 showed a significant increase at all time points ($P<0·01$), whereas in the AAA group TGF-β_1 showed no significant changes

Conclusion Endotoxaemia in patients undergoing TAAA repair is associated with monocyte suppression and a significant increase in the level of TGF-β_1. TGF-β_1 may play an important role in modulating the immune response to endotoxaemia associated with major aortic surgery.

Assessment of growth hormones and high-energy phosphates in mammary artery, saphenous vein and right atrial appendage in patients with coronary artery disease

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Background Noradrenaline (NA), angiotensin II (ATII) and endothelin (ET) are thought to be important growth factors in myocardium and vessels. It is likely that these factors play a role in the proliferation and migration of smooth muscle cells, which is thought to be the underlying mechanism in the occlusion of bypass grafts. One of the factors that may contribute to the activation and release of growth factors in hypoxia, unavoidable during preparation and transplantation of the vessels, which causes depletion of high-energy phosphates.

Aim This study was designed to examine the tissue content of growth hormones and of high-energy phosphates and their degradation products

Methods Some 40 patients with coronary artery disease undergoing elective coronary artery bypass surgery were studied.

Partial liquid ventilation redistributes pulmonary blood flow and total lung water

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Introduction Partial liquid ventilation (PLV) improves gas exchange in models of acute lung injury. The complete mechanisms are not yet elucidated. It is hypothesized that PLV redistributes regional pulmonary blood flow (PBF) and total lung water (TLW) from dependent regions toward non-dependent regions of the acutely injured lung, thereby improving gas exchange.

Methods The distribution of PBF and TLW was characterized in 16 adult dogs using positron emission tomography with $H_2{}^{15}O$. Measurements of gas exchange, PBF and TLW were made before and after lung injury was induced with intravenous oleic acid. They were repeated after 45 min of PLV with perflubron 30 ml kg^{-1} (LiquiVent, Alliance Corporation, San Diego, California, USA) ($n = 8$) and compared with gas-ventilated controls (GV) ($n = 8$) Regional data for PBF and TLW were analysed in three zones (I, II and III) from the non-dependent to the dependent aspects, and normalized to the activity of the whole lung Repeated-measures analysis of variance (ANOVA) and paired t tests were used within groups, and independent t tests were used between groups. Bonferroni correction defined significance at $P < 0{\cdot}025$. Data are expressed as mean(s.e.m.).

Results Transpulmonary shunt fraction decreased by 28(4) per cent after lung injury to 15(3) per cent during PLV (GV 26(2) to 37(5) per cent, $P < 0{\cdot}025$ within and between groups) During PLV, PBF and TLW redistributed from the dependent zone (III) toward the non-dependent zones (I and II). After injury, zone III had 43(3) per cent of PBF in the PLV group (GV 40(3) per cent), while during PLV zone III flow decreased to 36(1) per cent ($P < 0{\cdot}05$, ANOVA; $P < 0{\cdot}025$, within group, GV 35(2) per cent, P not significant between groups). Similarly, zone III had 40(1) per cent of TLW after injury in the PLV group (GV 41(2) per cent). During PLV, TLW decreased to 32(2) per cent ($P < 0{\cdot}001$, ANOVA; $P < 0{\cdot}001$, within group; CV 42(2) per cent, $P < 0{\cdot}001$ between groups).

Conclusion Gas exchange is improved during PLV. This is associated with redistribution of PBF and TLW from dependent regions toward non-dependent regions. These mechanisms may contribute to improved gas exchange during PLV in the setting of lung injury.

In vivo microcirculatory analysis of compartmental syndrome of striated skin muscle

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The compartmental syndrome is a common cause of functional impairment following trauma to the extremities. The central pathogenetic factor involved in the development of compartmental syndrome is increased tissue pressure, which compromises nutritive microcirculation, the ultimate cause of muscle cell necrosis. However, detailed information about the onset and course of compartmental syndrome, with special emphasis on microcirculatory events, is still not available. The aim of the present study was to analyse quantitatively muscle microcirculation in an *in vivo* model of repetitive compartmental syndrome.

The experiments were performed in Syrian golden hamsters using the dorsal skinfold chamber and intravital fluorescence microscopy for assessment of the striated skin muscle microcirculation, including A_2, A_3 and A_4 arterioles and nutritive capillaries as well as postcapillary and collecting venules ($n = 10$). The compartmental syndrome was induced with a balloon-tipped catheter which was fixed on the backside of the chamber and insufflated stepwise for controlled increase of pressure from 0 to 70 mmHg, followed by a stepwise balloon desufflation for pressure reduction from 70 to 0 mmHg This procedure for induction–release of compartmental pressure was repeated three times with simultaneous microscopic analysis of the identical region of interest. The following parameters were assessed: (i) occlusion and reopening pressure of arteriolar and venular vessels; (ii) arteriolar and venular vessel diameters; and (iii) number of perfused nutritive capillaries. Data are given as mean(s.e.m.) Statistical analysis was performed with analysis of variance followed by an appropriate pairwise comparison test.

Intravital fluorescence microscopy of striated skin muscle microcirculation revealed an arteriolar occlusion pressure of 28·9(5·0), 40·8(8·1), 39·3(4·3) and 65·0(2·2) mmHg for vessels with basal diameters smaller than 20, 40 and 60 μm and greater than 60 μm respectively. Reopening pressures with mean(s.e.m.) values of 26·6(5·1) (less than 20 μm), 29·0(7·2) (less than 40 μm), 28·0(4·3) (less than 60 μm) and 45·0(4·8) mmHg (greater than 60 μm) were in general lower ($P < 0{\cdot}05$) when compared with arteriolar occlusion pressure. At second and third induction of compartmental syndrome, both mean arteriolar occlusion and reopening pressures were significantly ($P < 0{\cdot}05$) lower in the arteriolar vessel class smaller than 20 μm Analysis of venules with diameters smaller than 20, 40 and 60 μm and greater than 60 μm respectively demonstrated occlusion pressures of 35·0(4·2), 32·1(3·4), 27·8(6·1) and 35·8(6·0) and reopening pressures of 24·9(3·9), 18(3·1), 23·3(3·7) and 23·9(4·3) mmHg respectively, however, no major changes followed repetitive compartmental syndrome. At a compartment pressure of 10 mmHg, the number of perfused capillaries was already reduced to 54·6(8·2) per cent, but remained unchanged with 59·8(4·9) and 52·8(7·5) per cent after the second and third induction of compartmental syndrome. At a higher pressure level of 25 mmHg, which, however, was below the pressure of arteriolar (less than 20 μm) occlusion, nutritive perfusion failure was found to be progressively ($P < 0{\cdot}05$) increased with only 35·8(9·8), 28·5(8·1) and 18·0(5·7) per cent perfused capillaries.

The present intravital microscopic study demonstrates that impairment of nutritive capillary perfusion appears, in comprison to arteriolar and venular microvascular segments, at remarkably lower pressure levels, which might be responsible for ischaemic muscle injury before manifestation of clinical symptoms. Moreover, microvascular perfusion of the smallest arterioles and nutritive capillaries seems to be particularly susceptible to repetitive induction of compartmental syndrome.

Herbimycin A, a tyrosine kinase inhibitor, attenuates ischaemia–reperfusion-induced microvascular injury

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Exposure of cells to a subcritical stress, such as hyperthermia, (thermotolerance) protects cells from subsequent injury by inducing 72-kDa heat shock protein (HSP72) expression *in vitro*. The objective of this study was to investigate a pharmacological approach to HSP72 induction and endothelial protection. Herbimycin A (HA) is a benzoquinoid ansamycin antibiotic which inactivates p60$^{v\text{-}src}$ tyrosine kinase. It has been demonstrated to induce HSP72 in cell culture, but its effects *in vivo* are unknown. Sixteen Sprague-Dawley rats were randomized into sham ischaemia–reperfusion (I–R), I–R, and HA plus I–R groups. HA (100 μg per rat) was administered 18 h before to I–R injury I–R injury was established by occlusion of the superior mesenteric vascular pedicle for 10 min, followed by 60 min of reperfusion. The numbers of adherent and migrated leucocytes, and their rolling velocity, were measured by intravital microscopy in a postcapillary venule (25–35 μm) at baseline (−10 min), ischaemia (0 min), and 10, 30 and 60 min after reperfusion. HSP72 expression in mesentery, intestine and lung was determined by Western immunoblotting In this model, induction of ischaemia resulted in a 90 per cent reduction in blood flow.

Methods Rats on the MCDD were compared with 24 animals fed a normal diet (ND). Both groups were fed the diet for 28 days before single-lobe liver ischaemia. The left liver lobe of each rat was cross-clamped for either 15, 30, 60, 75, 90 or 120 min It was revascularized, rats were recovered and kept on either diet for 7 days, at which time they were killed and the liver was removed Liver weights were compared with those of control rats, and sections were taken for histological examination from non-ischaemic and ischaemic liver lobes of all rats.

Results Fatty liver changes were induced by the use of a MCDD in Wistar rats No significant weight loss occurred in MCDD-fed rats (mean(s.d.) 357(96) g to 326(88) g, $P = 0.3$) or ND-fed rats (35(76) g to 360(75) g, $P = 0.8$). Liver weight was not significantly different between MCDD-fed (17.3(1.6) g) and ND-fed (17.5(1.6) g) rats ($P = 0.78$), however, liver histology of all MCDD rats demonstrated changes consistent with fatty liver disease (from + to ++ macrovesicular steatosis). Changes were markedly accentuated following ischaemic injury in MCDD rats with microvesicular steatosis apparent after 75 min of ischaemia. Consistent ischaemic damage occurred with more than 30 min of ischaemia, including portal fibrosis, venular fibrosis, focal lobular necrosis and portal inflammation. Ischaemic damage was proportional to the length of ischaemia with disruption of the vasculature, bridging fibrosis, focal cirrhosis, necrosis and vascular congestion evident at over 90 min.

Conclusion Provision of a MCDD is a reliable means to induce fatty liver hepatitis. Ischaemia in fatty liver causes severe fibrosis and portal tract damage with a period of ischaemia considerably shorter than that required to induce comparable damage in normal liver.

Effect of ischaemia–reperfusion on neutrophil phagocytosis and CD16 receptor expression

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Background Following ischaemia–reperfusion (I–R), polymorphonuclear neutrophils (PMNs) are 'superactivated', however, patients still develop postoperative infective complications. The aim of this study was to examine the relationship between the expression of the PMN receptor for phagocytosis, FcγRIII (CD16), and PMN ability to phagocytose following I–R

Methods Thirty patients, 19 men and 11 women, undergoing femorodistal surgery for critical ischaemia were studied and assessed for infective complications. Blood was taken before operation and following reperfusion for 7 days. CD16 expression was measured unstimulated and following stimulation with phorbol myristate acetate (PMA), formyl-methionyl-leucyl-phenylalanine (fMLP), tumour necrosis factor (TNF) and lipopolysaccharide (LPS)

Results Values are expressed as median (interquartile range) Phagocytosis decreased in all patients following I–R, although patients with infective complications had a significantly greater fall in phagocytosis (from 149 (125–157) to 82.5 (78–97) *versus* 144 (121–159) to 123 (107–130) in the non-infective group, $P < 0.05$, Mann–Whitney U test).

	CD16 MCF				
	Control	fMLP	LPS	TNF	PMA
Before operation					
Infective	113*	160*	151	165	194
Non-infective	52*	72*	70	75	80
Day 1					
Infective	22	15†	16	13	11
Non-infective	25	46†	47	53	61

*$P < 0.05$ *versus* control (Wilcoxon matched pairs), †$P < 0.05$ *versus* control (Mann–Whitney U test)

Conclusion All patients undergoing I–R develop impaired PMN phagocytosis, with a greater decrease in those developing infective complications CD16 expression was greater before operation in patients who developed infective complications Both groups showed a fall in CD16 expression following I–R, however, patients who developed complications demonstrated a further decrease following stimulation. This may help to explain why patients with 'superactivated' PMNs following I–R develop infective complications.

Lack of capillary flowmotion after osteomyocutaneous free flap transfer: potential mechanism of free flap failure

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Introduction In clinical practice loss of osteomyocutaneous free flaps may occur despite anastomotic patency. Flowmotion, i.e. rhythmic fluctuations of capillary blood flow caused by arterial vasomotion, is hypothesized to be a local mechanism for maintaining adequate microvascular blood perfusion under conditions of critical ischaemia. However, it is not known yet whether flowmotion–vasomotion also protects critically perfused osteomyocutaneous free flaps, or whether these mechanisms are lost because of the free flap transfer. The purpose of this study was to elucidate capillary flowmotion in an osteomyocutaneous free flap model using intravital microscopic techniques.

Methods Dextran-insensitive Wistar rats ($n = 14$) were used. With pentobarbital anaesthesia (50 mg per kg body-weight intraperitoneally), a circular skin island on the anteromedial aspect of the left hindlimb was shaved and circumcised. The proximal and distal end of the tibial bone was cut and the lateral and dorsal aspects of the bone segment were dissected free. The anteromedial aspect connected with the gracilis and semitendinosus muscles were left without manipulation. The muscles were cut proximally at their medial aspects and dissection of the femoral vessels to the inguinal ligament guaranteed all blood flow to the newly formed osteomyocutaneous flap, which finally consisted of the tibia segment, the two muscles, and the overlying subcutis and skin. Exterioration of the flap allowed for intravital fluorescence microscopic study (5 per cent FITC dextran, mol wt. 150 000, intravenously) of muscle, skin, subcutis and periostal tissue. Critical perfusion conditions were induced by a micromanipulator-controlled ligature at the femoral artery and were controlled by an ultrasonic flowmeter. In six animals the osteomyocutaneous flap was transferred to the contralateral hindlimb and anastomosed end-to-end to the right femoral vessels Non-transferred flaps, which remained *in situ* ($n = 8$), served as controls.

Results In non-transferred flaps, stepwise reduction of femoral blood from 0.22 to 0.15 ml min^{-1} induced in all animals capillary flowmotion in muscle, but not in periostal, subcutis and skin tissue. Flowmotion persisted at 0.10 ml min^{-1} but disappeared at further reduction of femoral blood flow to 0.05 ml min^{-1}. During both, baseline conditions and flowmotion, muscle capillary perfusion failure was not detectable. However, the disappearance of flowmotion (0.05 ml min^{-1} femoral blood flow) was associated with marked capillary perfusion deficits (77 per cent, $P < 0.05$). Autonomic denervation by cutting the femoral nerve did not change the flowmotion pattern In contrast, after flap transfer, flowmotion could not be observed at any stage of flow reduction, which progressively increased muscle capillary perfusion failure (0.15 ml min^{-1}), 10 per cent; 0.10 ml min^{-1}, 25 per cent; 0.05 ml min^{-1}, 60 per cent)

Conclusion This study indicates that osteomyocutaneous free flaps do not have the potential to counteract compromised flow conditions by muscle capillary flowmotion. The lack of inducibility of flowmotion may be related to ischaemia-reperfusion-associated mechanisms rather than to the lack of autonomic innervation after transfer

($n = 5$), Dex-CDH ($n = 5$) and NS-nonCDH ($n = 5$). Quantification was performed by laser densitometry.

Results On day 20·5 of gestation, NS-CDH rats had a 30 per cent reduction in eNOS expression compared with OO-NS controls ($P = 0{\cdot}01$). Dex-CDH animals at day 20·5 showed significantly higher eNOS expression than CDH rats ($P = 0{\cdot}01$) and had levels equivalent to those of normal controls. At term (day 21·5) no difference in eNOS expression was detected between the groups.

Conclusion There is a deficiency of eNOS near term (day 20·5) in CDH fetal rats. Dexamethasone therapy restores eNOS expression in these animals to levels seen in the lungs of normal controls. This could have implications for the therapeutic manipulation of fetal pulmonary vascular reactivity. However, at term, the precise role of eNOS in the pathophysiology of pulmonary hypertension in this CDH model remains uncertain. Further studies are required to understand the regulatory mechanisms governing eNOS expression and nitric oxide activity.

Impaired apoptotic death signalling in inflammatory lung neutrophils is associated with decreased expression of interleukin 1*β* converting enzyme

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Background Fas and tumour necrosis factor receptor 1 (TNFR1) are membrane proteins that signal for apoptotic cell death by downstream activation of proteins of the interleukin 1*β* converting enzyme (ICE) family; engagement of these receptors induces apoptosis. The authors have shown that spontaneous apoptosis is delayed in polymorphonuclear neutrophil (PMN)–activated by transmigration into an inflammatory focus. The present study was undertaken to evaluate the effects of transmigration on Fas and TNFR1-induced apoptosis and apoptotic gene expression.

Methods Sprague-Dawley rats were killed 4 h after intratracheal challenge with 500 μg lipopolysaccharide (LPS). PMNs were isolated from whole blood (WB) and bronchoalveolar lavage fluid (BAL) of LPS-treated animals by density centrifugation and incubated with or without anti-Fas (clone CH-11, 100 ng ml^{-1}) or TNF (10 ng ml^{-1}) for 24 h. Apoptosis was assessed by flow cytometry using propidium iodide DNA staining, and confirmed morphologically. Fas expression was evaluated using FITC anti-Fas (UB2, 4 μg ml^{-1}). ICE and Bcl-2 protein were measured by Western blot analysis using mouse antihuman antibodies.

Results BAL PMNs showed delayed apoptosis compared with WB PMNs and failed to undergo apoptosis in response to Fas and TNF.

	Con	Fas	TNF
BAL	22(10)	20(8)	14(11)
WB	44(6)*	65(7)*†	68(10)*†

Values are mean(s.d.) percentage apoptosis. $^*P < 0{\cdot}05$ *versus* BAL, $^\dagger P < 0{\cdot}05$ *versus* WB Con

Fas expression on WB and BAL PMNs was similar (4·3(0·9) and 4·0(0·2) LnMCF respectively). BAL PMNs showed a decrease in both the pro and active form of ICE. Bcl-2 was not detected in either group.

Conclusion Transmigrated PMNs show reduced spontaneous apoptosis and are resistant to cell death signals delivered through Fas and TNFR1 in association with reduced levels of both pro and active ICE protein. Altered responsiveness to physiological apoptotic stimuli prolongs PMN functional survival during acute inflammation and may contribute to the tissue injury of adult respiratory distress syndrome.

Induction of a heat shock response protects against Fas-mediated lethality in mice through attenuation of hepatocyte injury

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Introduction Stimulation of the Fas/APO-1 receptor elicits a process of programmed cell death. Injection of anti-Fas monoclonal antibody (mAb) into mice has been found to cause liver destruction resulting from massive hepatocyte apoptosis. Previous studies have demonstrated that induction of a heat shock response is cytoprotective against a variety of noxious stimuli. However, it is unknown whether induction of a heat shock response is beneficial or detrimental in Fas-mediated hepatocyte apoptosis.

Aims The aims of this study were to evaluate the effect of heat shock on Fas-mediated hepatocyte apoptosis and subsequent liver destruction.

Methods CD-1 mice were randomized into four groups ($n = 8$ per group): saline as control, heat shock alone, Fas mAb (Jo2) alone (2·5 mg per mouse intravenously), and heat shock plus Fas mAb. Heat shock in mice was induced by maintaining rectal temperature at 41 ± 5°C for 15 min, and 18 h before anti-Fas mAb injection. The induction of apoptosis in liver was determined using the *in situ* TUNEL technique, enzyme-linked immunosorbent assay (ELISA) and DNA gel electrophoresis. Hepatic damage was evaluated by measuring hepatic enzyme levels in serum and by histology. Heat shock protein 72 expression in hepatic tissue was detected by Western immunoblotting.

	Saline	Heat shock	Fas mAB	Heat Fas mAB
DNA fragments	100(35)	93(19)	1189(273)*	342(117)*†
ASAT (units ml^{-1})	84(20)	85(27)	532(137)*	130(48)*†
SGPT (units ml^{-1})	65(9)	75(25)	304(80)*	117(38)*†

Values are mean(s.d.). ASAT, aspartate aminotransferase; SGPT, serum glutamic–pyruvic transaminase. $^*P < 0{\cdot}05$ *versus* saline, $^\dagger P < 0{\cdot}05$ *versus* Fas mAb (analysis of variance)

Results Injection of mice with anti-Fas mAb resulted in significant increases in hepatocyte apoptosis and DNA fragmentation as confirmed by *in situ* TUNEL, ELISA and DNA gel electrophoresis. Furthermore, Fas mAb caused hepatic damage as represented by an increase in serum levels of ASAT and SGPT. Induction of a heat shock response in mice, as confirmed by heat shock protein 72 expression in liver, significantly attenuated Fas mAb-induced hepatocyte apoptosis and DNA fragmentation, and reduced hepatic enzyme release. Moreover, induction of a heat shock response significantly ameliorated the mortality rate (17 *versus* 67 per cent, $P < 0{\cdot}05$) induced by the lethal dose of Fas mAb (5 mg per mouse intravenously) in mice.

Conclusion These results demonstrate that induction of a heat shock response can ameliorate liver destruction associated with Fas-induced hepatocyte apoptosis and attenuate Fas-mediated lethality.

Fatty liver increases susceptibility to ischaemic injury

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Background Fatty liver has been postulated as a cause of primary non-function following ischaemia in liver transplantation. In this study the use of a methionine and choline-deficient diet (MCDD) to induce fatty liver changes was investigated in 24 Wistar rats and the effect of segmental liver ischaemia on fatty liver was assessed.

repeated with the protein kinase C inhibitor, calphostin (0–100 μmol l^{-1})

	Nitrite	NOS2 mRNA
LPS	145(3·2)	0·54(0·08)
LPS + calphostin (10 μmol l^{-1})	103(7·3)*	
LPS + calphostin (50 μmol l^{-1})	68·6(4·5)*	
LPS + calphostin (100 μmol l^{-1})	35·4(6·1)*	0·17(0·08)†

$^{*}P = 0·001$ (ANOVA), $^{†}P < 0·01$ *versus* LPS

These data indicate that inhibition of trimeric G protein and G_q subunit associated protein kinase C activities decreases nitric oxide synthesis and NOS2 mRNA levels. In ANA-1 macrophages, LPS-mediated nitric oxide synthesis is dependent on trimeric G_q protein–protein kinase C signal transduction

Surgical trauma triggers neutrophil apoptosis

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Aim Alteration in proinflammatory cell kinetics has been implicated in the development of sepsis in the postoperative patient It has also been shown that neutrophils undergoing apoptosis are functionally effete and have poor microbicidal capability. Thus the aim of this study was to examine the effect that elective surgery may have on neutrophil function and programmed cell death in this early postoperative period.

Methods Whole blood was harvested at T_0, T_2, T_6, T_{12}, T_{18}, T_{24} and T_{48} h, where T_0 equals the time of initiating surgery. This was analysed for systemic neutrophil count, superoxide respiratory burst activity (denotes neutrophil function) and CD11b/CD16 (markers of apoptosis) via flow cytometry.

	T_0	T_2	T_6	T_{12}	T_{18}	T_{24}	T_{48}
CD11b	154(20)	166(31)	241(34)*	199(21)*	172(22)	161(21)	178(34)
RBA	163(41)	152(41)	120(49)	93(45)*	153(69)	85(31)*	102(36)
CD16	115(29)	120(10)	68(13)*	69(17)*	73(13)*	80(5)	81(27)

Values are mean(s.e.m.) channel fluorescence $^{*}P < 0·05$

Results Neutrophilia occurred between 6 and 12 h after operation. Neutrophil CD11b receptor expression was upregulated between 6 and 12 h after operation ($P < 0·05$). CD16 receptor expression was downregulated at 6 h and remained significantly downregulated until 24 h after operation ($P < 0·05$) Superoxide respiratory burst activity was also significantly downregulated 12 h ($P < 0·05$) The postoperative neutrophil apoptotic rate was increased at 6 h after surgery relative to preoperative values.

Conclusion Elective surgery resulted in a significant increase in systemic neutrophil programmed cell death, a finding that may also account for defective oxidant activity. These results demonstrate for the first time that injury programmes proinflammatory cells for early death and may represent a significant development in our understanding of postoperative sepsis.

The neutrophil CD16 receptor in patients with postoperative sepsis is defective

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Introduction The cleavable glycan-phosphatidyl-inositol-linked neutrophil receptor FcγRIIIb (CD16) is overexpressed in patients likely to develop postoperative sepsis Cleaved (free) CD16 acts as a circulatory opsonin. The aim was to determine whether this overexpression is consequent on a positive feedback loop due to a structural defect or to defective cleavage of the receptor.

Methods Sixty-five patients (34 men; mean age 58 (range 35–89) years) undergoing elective surgery for benign and malignant gastrointestinal disease were studied. Twelve patients had a septic postoperative course as determined by standard criteria. Blood for polymorphonuclear neutrophil (PMN) harvesting and serum were obtained from each patient before operation and on successive postoperative days Neutrophils were incubated with rhodamine–phycoerythrin-conjugated anti-CD16 monoclonal antibody, and cell-bound CD16 expression was determined by flow cytometry (mean channel fluorescence (MCF00)). Serum-soluble CD16 was measured in arbitrary units by immunoblotting and enhanced chemiluminescence, and analysed on an optical densitometer The serum levels of interleukin (IL) 10 and tumour necrosis factor (TNF) α (downregulator and upregulator of CD16 respectively) were estimated concomitantly by standard methods.

Results The electrophoretic mobility of free CD16, as determined by Western blotting, was found to be similar in both groups indicating that there was no structural difference.

	Septic patients ($n = 12$)	Non-septic patients ($n = 53$)
PMN CD16 (MCF)	2993(267)* preop.	837(54) preop.
Free CD16 (units)	23·4(1·2) postop.	19·7(1·9) postop.
IL-10 (pg ml^{-1})	5·8(0·6) postop.	6·2(1·1) postop.
TNF-α (pg ml^{-1})	47·3(2·4)* postop.	17·7(1·8) postop.

Values are mean(s.d.). $^{*}P < 0·001$ septic *versus* non-septic patients (Mann–Whitney *U* test)

Conclusion Similar levels of free CD16 in both groups suggest that in septic patients the overexpressed PMN CD16 is non-cleavable and cannot be released to act as an opsonizing agent. This defective mechanism may account for the occurrence of unexpected postoperative sepsis.

Dexamethasone increases expression of endothelial nitric oxide synthase in fetal lungs of rats with congenital diaphragmatic hernia

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Background The current mortality rate from congenital diaphragmatic hernia (CDH) remains high owing to a lethal combination of pulmonary hypoplasia and pulmonary hypertension Prenatal glucocorticoid therapy has been shown to improve biochemical immaturity, lung compliance and morphology in experimental animals with CDH. Endothelium-derived nitric oxide synthase (eNOS) produces nitric oxide, a potent pulmonary vasodilator. A deficiency of nitric oxide is implicated in the pathogenesis of CDH-related pulmonary hypertension. The aim of this study was to examine the expression of eNOS as a marker of the glucocorticoid effect on pulmonary vascular reactivity in rats with CDH.

Method CDH was induced in fetal rats by the maternal administration of 100 mg Nitrofen on day 9·5 of gestation (term is day 22). Control animals received olive oil (OO) by gavage. Dexamethasone (Dex) (0·25 mg kg^{-1}) or normal saline (NS) was given by intraperitoneal injection on days 18·5 and 19·5 before delivery of the fetuses by caesarean section on days 20·5 and 21·5. eNOS protein expression was studied by Western immunoblotting on the lungs of five animals from each of four experimental treatment groups: OO-NS ($n = 5$), NS-CDH

Clinically, of 280 patients treated with living related liver transplantation, ten including six adults, receiving a small graft underwent APOLT from living donors (four liver cirrhosis, two Wilson's disease, two fulminant hepatic failure, two ornithine transcarbamylase deficiency). Doppler ultrasonography revealed good PF to the graft in seven recipients. Of three recipients with insufficient PF to the graft, one (fulminant hepatic failure) underwent resection of the remnant native liver and two (one liver cirrhosis, one fulminant hepatic failure) died from infection. One recipient with liver cirrhosis died from bleeding. This study suggests that APOLT could be a useful option in liver transplantation.

Physiology of temperature balance during laparoscopy

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This experimental study evaluated whether humidification of warmed insufflated carbon dioxide during laparoscopic procedures would resolve the problem of laparoscopy-induced hypothermia.

Core temperature changes in five anaesthetized pigs were measured over a 3-h period. Animals were allocated randomly to insufflation at $10\,l\,min^{-1}$ with either cool dry carbon dioxide gas, heated humidified carbon dioxide gas, or no gas. Each animal was therefore studied on three separate occasions, acting as its own control.

Core temperatures after insufflation with heated humidified gas were no different from those in controls. After insufflation with cool dry gas, core temperature dropped by 1·77°C, significantly more than the 0·6°C drop experienced by control animals and those insufflated with heated humidified gas ($P < 0{\cdot}01$).

Thermodynamic calculations of the heat expended in evaporation of water were also performed. The temperature drop due to water evaporation alone in pigs insufflated with cool dry gas was calculated to be 1·2°C. This compared favourably with the measured 1·17°C temperature difference between these animals and those in the control group.

These data confirm that the majority of heat lost during laparoscopic insufflation is due to water evaporation, and this can be prevented by using heated and humidified insufflated gas.

Haemofiltration neutralizes sepsis mediators in the course of pancreatitis

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Aim The purpose of the study was to investigate whether the beneficial effect of continuous venovenous haemofiltration (CVVHF) in severe pancreatitis reported in recent studies could be related to decreased plasma concentrations of sepsis-associated mediators.

Methods Fasted pigs were anaesthesized with piritramide ($0{\cdot}8\,mg\,kg^{-1}\,h^{-1}$), midazolam ($0{\cdot}3\,mg\,kg^{-1}\,h^{-1}$) and pancuronium ($0{\cdot}2\,mg\,h^{-1}\,kg^{-1}$). Pancreatitis was induced by injection of sodium taurocholate (5 per cent, $1\,mg\,kg^{-1}$) and enterokinase ($5\,units\,kg^{-1}$) in the pancreatic duct. CVVHF was performed by placement of two Sheldon catheters in both femoral veins. Group 1 animals ($n = 10$) received no further treatment other than fluid replacement. In group 2 ($n = 10$), CVVHF was started after arterial pressure decreased 20 per cent below baseline values. In group 3 ($n = 9$), animals underwent CVVHF immediately after induction of pancreatitis. Recorded haemodynamic parameters included mean arterial pressure, cardiac output, heart rate and survival time (Kaplan–Meier). Biochemical parameters detected were protein concentration in plasma, haematocrit, kinin (radioimmunoassay) and leucocyte neutral proteinase inhibitor (LNPI, by enzyme-linked immunosorbent assay).

Results Mean(s.d.) survival time in controls was 6·4(1·9) h. CVVHF in treatment groups resulted in a significant prolongation of survival time (10·9(2·1) h in group 2, $P < 0{\cdot}05$; 12·6(2·4) h in group 3, $P < 0{\cdot}01$). As a result of protein shift with consecutive fluid loss from the intravascular to the extravascular compartment, intravascular hypovolaemia occurred. At the respective times of measurement, both impairment of haemodynamic parameters and haemoconcentration indicating capillary leak syndrome were significantly weakened in groups 2 and 3 compared with controls. At 4 h postinduction, no relevant differences between groups in the increase of kinin concentrations in ascites could be detected (680 per cent in group 1, 820 per cent in group 2 and 750 per cent in group 3). However, kinin levels in plasma increased significantly less in treatment groups than in controls. A similar feature – a comparable increase of concentration in ascites *versus* a higher increase in plasma in controls compared with groups 2 and 3 – could be demonstrated for LNPI.

Conclusion CVVHF significantly improves survival in experimental acute pancreatitis, indicating at least partial neutralization of sepsis-related mediators during CVVHF.

Endotoxin-mediated synthesis of nitric oxide is dependent on G_q protein signal transduction

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Endotoxin (lipopolysaccharide (LPS))-mediated production of nitric oxide in macrophages is associated with a variety of cellular functions. Although the molecular biology and enzymology of nitric oxide synthesis are well characterized, little is known of the signal transduction pathway by which LPS induces nitrix oxide production. To investigate this pathway. Nitric oxide production was induced in antinuclear antibody (ANA) 1 macrophages by LPS ($10\,\mu g\,ml^{-1}$). LPS-treated cells were incubated with inhibitors of tyrosine kinase (genistein $0–10\,\mu mol\,l^{-1}$ or tyrophostin $0–100\,\mu mol\,l^{-1}$) and trimeric G protein (suramin $0–50\,\mu mol\,l^{-1}$ or GOTP $0–500\,\mu mol\,l^{-1}$). The nitric oxide metabolite, nitrite ($nmol\,mg^{-1}$), was assayed in the culture medium. Steady-state levels of nitric oxide synthetase (NOS) 2 messenger RNA (mRNA) were determined with reverse transcriptase–polymerase chain reaction and expressed relative to β-actin mRNA. In the presence and absence of inhibitors, unstimulated cells exhibited minimal nitrite production (mean(s.e.m.) 12·1(2·3) $mm\,mg^{-1}$) and no inducible NOS (iNOS) mRNA. Inhibitors were not cytotoxic, as determined by lactate dehydrogenase release. (Data are presented as mean(s.e.m.), $n = 4$. Statistical analysis was performed with one-way analysis of variance (ANOVA) or the Mann–Whitney *U* test, as appropriate.)

	Nitrite	NOS2 mRNA
LPS	145(3·2)	0·54(0·08)
LPS + suramin 1 $\mu mol\,l^{-1}$)	92·7(4·2)*	0 22(0·06)†
LPS + suramin (10 $\mu mol\,l^{-1}$)	46·9(3·6)*	
LPS + suramin (50 $\mu mol\,l^{-1}$)	31·0(3·9)*	0·03(0·02)†
LPS + GOTP (10 $\mu mol\,l^{-1}$)	130(8 3)*	0·35(0·04)†
LPS + GOTP (100 $\mu mol\,l^{-1}$)	71·3(6·2)*	
LPS + GOTP (500 $\mu mol\,l^{-1}$)	38·1(3·3)*	0·11(0·03)§

*$P = 0{\cdot}001$ (ANOVA), †$P < 0{\cdot}01$ *versus* LPS, ‡$P < 0{\cdot}01$ *versus* $1\,\mu mol\,l^{-1}$ suramin, §$P < 0{\cdot}01$ *versus* $10\,\mu mol\,l^{-1}$ GOTP

Tyrosine kinase inhibition did not alter nitrite or NOS2 mRNA levels. To determine whether the G_q subunit class mediated LPS-induced nitrix oxide production, studies were endotoxaemia compared with BG22 and irrelevant peptide (BG16) was tested.

Results Compared with BG16 and BG22, the hybrid peptide BU3 demonstrated. (1) binding to LPS similar to that of BPI (not shown); (2) increased endotoxin neutralization but not bactericidal activity (*Table*); and (3) potent *in vivo* endotoxin neutralization (*Figure*) in a murine model of *P. aeruginosa* endotoxaemia.

Conclusion These data support the contention that it is possible to enhance LPS binding and biological activity of an endotoxin antagonist via stabilization of peptide structure. These data should facilitate the design of even more potent endotoxin antagonists that could have great potential for use in treating Gram-negative bacterial sepsis

Involvement of Fas–Fas ligand interaction in CD28-independent pathway of allogeneic hepatocyte rejection

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Cytolytic induction of T cells requires both T cell receptor (TCR)-mediated antigenic stimulation and the CD28-mediated costimulatory signal. Blockade of the interactions between CD28 and its ligands, CD80 and CD86, prolongs the survival of allografts in some transplant models. However, the authors have found that allogeneic hepatocytes are completely rejected within 7 days after intrasplenic transplantation even when treated with monoclonal antibodies (mAbs) against CD80 and CD86 (anti-CD80/86) Recent studies have shown that there are two main mechanisms of T cell-mediated cytotoxicity, perforin- and Fas-based ones. It has been demonstrated that the liver is highly sensitive to Fas ligand (FasL), which can be produced by T cells independently of CD28 costimulation. The aim of this study was to clarify the role of the Fas–FasL system in the allogeneic hepatocyte rejection.

Fas-deficient hepatocytes were transplanted into the spleen of allogeneic recipients, and Fas-bearing hepatocytes were transplanted into the spleen of allogeneic FasL-deficient recipients with or without the anti-CD80/86 mAb treatment. The cytotoxic activity of FasL-deficient splenic T cells which had been stimulated by allogeneic splenocytes in the presence or absence of anti-CD80/86 mAbs was examined.

With the anti-CD80/86 mAb treatment, Fas-deficient hepatocytes could survive for 7 days after transplantation, and Fas-bearing hepatocytes could also survive for 7 days in the spleen of FasL-deficient mice CD28-independent induction of cytotoxicity against allogeneic hepatocytes was not observed when the effector cells were derived from FasL-deficient mice

The Fas–FasL system plays a critical role in the CD28-independent pathway of allogeneic hepatocyte rejection.

Clinical application of dynamic magnetic resonance mammography: evaluation of 622 scans

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Dynamic contrast-enhanced magnetic resonance mammography (MRM) is an emerging breast imaging modality The authors have previously presented their preliminary results, which showed dynamic MRM to be sensitive and specific for the diagnosis of primary and recurrent breast cancer and in the evaluation of response to neoadjuvant treatment. Their total experience with dynamic contrast-enhanced MRM is presented

Protocols were designed to investigate the clinical role of MRM in the diagnosis of primary breast lesions, in the follow-up of patients after breast-conserving therapy or reconstruction, and in monitoring the response to neoadjuvant therapy The sensitivity and specificity of MRM were compared with traditional methods of assessment. Following MRM, patients were monitored with traditional diagnostic modalities according to standard guidelines.

A total of 622 dynamic MRM scans were performed on 572 patients: primary breast lesions ($n = 352$), following local surgery ($n = 217$), following prosthetic reconstruction ($n = 26$) and monitoring the response to neoadjuvant therapy ($n = 27$). MRM produced a sensitivity and specificity of 100 and 96 per cent respectively for the detection of primary malignancy, with a 100 per cent sensitivity for the diagnosis of histologically confirmed multifocal disease as opposed to 22 per cent for mammography All recurrent malignancy was detected with MRM with a specificity of 93 per cent compared with 67 per cent for standard triple assessment MRM proved the only reliable method for the detection of viable tumour following neoadjuvant therapy.

This series represents the largest UK experience and clearly demonstrates that dynamic MRM should now be used routinely for monitoring the response to neoadjuvant therapy and for the evaluation of patients with either primary lesions or post-cancer therapy breasts that are equivocal on traditional investigations

Study of portal flow and regeneration in auxiliary partial orthotopic liver transplantation

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Purpose In auxiliary heterotopic liver transplantation, it was reported that banding of the portal vein (PV) to the native liver was mandatory to obtain sufficient portal flow (PF) to the graft. An investigation was made of how the presence of PF to the native liver influenced PF and regeneration of the native liver and graft in auxiliary partial orthotopic liver transplantation (APOLT)

Methods Beagle dogs (mean(s.d.) weight 11·4(0·3) kg) were used as donors and recipients. The left two lobes of donor livers (43·5(1·1) per cent of the whole liver and 1·1(0·05) per cent recipient body-weight (BW)) were transplanted orthotopically into the recipients after partial hepatectomy except for the right two lobes (77·5 per cent resection). The recipients were divided into two groups. In the ligated group (LG) ($n = 7$) the PV to the native liver was ligated. In the preserved group (PG) ($n = 4$) the PV was not ligated. PF was measured serially by an ultrasonic blood flowmeter placed at the PV trunk and at the left PV to the graft. Liver function was assessed by blood chemistry. On postoperative day 5, surviving dogs were killed, and the regeneration of the native liver and graft was evaluated by uptake of 5-bromodeoxyuridine (BrdU) and hepatic weight gain (liver weight on postoperative day 5/at operation).

Results and conclusion Two dogs in the LG died before postoperative day 5, and hepatic chemistry findings in the LG were higher than those in the PG. Mean(s.d.) PF to the graft (ml per min per kg body-weight) increased transiently after ligation of the PV to the native liver (PG 9·1(1·6), LG 18·4(2·1)), but there was no significant difference between the two groups on postoperative day 5 (PG 10·3(2·0), LG 14·1(0·2)). PF both to the native liver and to the graft in the PG was maintained throughout the experiment (graft PF/total PF was 33·2(4·4) per cent just after portal reflow and 30·2(9·8) per cent on postoperative day 5). The percentage of BrdU-labelled cells and hepatic weight gain in the graft were not significantly different between the two groups (PG 2·1(0·5) and 166(11) per cent, LG 3·1(0·7) and 202(29) per cent respectively). On the other hand, the native liver weight gain in the PG (256(28) per cent) was significantly higher than that in the LG (168(21) per cent). In summary, good PF and regeneration in both the native liver and graft were observed in APOLT with preservation of PF to the native liver.

mRNA	AAA (μg per μg GAPDH)	Normal aorta (μg per μg GAPDH)	*P*
MMP-1	3·64(0·88)	0·43(0·17)	0·027
MMP-2	29·12(5·46)	16·56(5·59)	n.s.
MMP-9	78·03(21·49)	3·35(0·90)	0·003
TIMP-1	835·32(92 74)	477·2(94·30)	0·027
TIMP-2	18·09(3·26)	4·14(0·65)	0·003
MMP-1/ TIMP-1	0·0039(0·00055)	0 00089(0·00024)	0·005
MMP-9/ TIMP-1	0·094(0·023)	0·0092(0·0041)	0·004

n.s., Not significant

Conclusion Increases in expression of MMP-1, MMP-9 and MMP/TIMP ratios may result in the increased proteolysis and matrix degradation that characterize AAAs. MMP-9 appears to be the predominant metalloproteinase expressed in AAAs, as its mRNA levels were more than 20 times and two times higher than those of MMP-1 and MMP-2 respectively. The molar excess of TIMP mRNA levels compared with those of MMPs suggests that localized differences in relative levels within the aortic wall may be extremely important in the pathogenesis of AAA.

Slow transit constipation: a sporadic or hereditary neuropathy?

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Background Idiopathic slow-transit constipation (STC) may be the result of a systemic autonomic or small sensory fibre neuropathy. Thirty-one constipated patients (30 women) and 20 age- and sex-matched controls were tested using new selective methods of quantitative peripheral sensory and autonomic motor testing. The study also included nine diabetic patients with established autonomic gastrointestinal involvement as a model group.

Results Six patients had a strong family history of functional bowel disease: idiopathic constipation requiring medical intervention ($n=5$, including identical twins) and Hirschprung's disease (HD) ($n=2$). The main significant abnormal findings are shown in the *Table*. Subgroups with abnormalities were defined as more than two standard deviations from the control mean. These data show subgroups of STC cases with marked autonomic or sensory abnormalities.

Test	Controls	STC normal	STC with abnormality	Diabetic abnormality
Autonomic tests				
Axon reflex sweating (nerve mediated) (g m^{-2} h)	$n=20$ 32–84 (47)	$n=22$ 35–74 (42) n.s	$n=9$ 7 22 (13) $P<0\ 0001$	$n=4$ 4–20 (15) $P=0\ 002$
Direct sweating (gland) (g m^{-2} h)	$n=10$ 42–72 (62)	—	$n=9$ 33–87 (56)	—
Small fibre sensory tests				
Thermal threshold: cool (δT°C)	$n=20$ 1 0–3·5 (1 5)	$n=23$ 0 9–4 3 (2 0) n s.	$n=8$ 2 2–5·6 (2·3) $P=0\ 001$	$n=8$ 2 2–18 (14) $P=0\ 0002$
Thermal threshold· warm (δT°C)	$n=20$ 2 0–4 8 (3·1)	$n=23$ 2 0–5 0 (4 0) n s	$n=8$ 5 2–12 1 (6 9) $P<0\ 0001$	$n=8$ 3 5–18 (15 6) $P=0\ 0006$

Values are range (median) n.s., Not significant (Mann–Whitney *U* test)

Two patients from the STC group with sensory abnormalities also showed reduced axon reflex vasodilatation (nociceptive function). Four of the eight patients with sensory abnormality had decreased rectal sensation. Five of nine patients with autonomic disturbance were in cases with familial association. All cases that required surgery (six of 31) had abnormalities on testing. These abnormal findings were similar to those in the diabetics, three of whom had no evidence of neuropathy on bedside clinical examination.

Conclusion A subgroup of STC cases has clear evidence of neuropathy only on quantitative tests, with some similarity to diabetics. The familial association, especially with HD, suggests a genetic basis that deserves further investigation. The abnormal findings in the cases that required surgery suggests that such neuropathy may be a bad prognostic indicator.

Design of a potent novel endotoxin antagonist

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Background A β-sheet conformation has been predicted for the lipopolysaccharide (LPS, endotoxin) binding domain (amino acids 82–108) of bactericidal permeability increasing protein (BPI), a host defence protein that binds with high affinity to and neutralizes LPS, and is also bactericidal. Peptide sequences derived from this region (BG22) also bind to and neutralize LPS, although less effectively, and this may be the result of their random coil structure in solution. The purpose of this study was to determine whether improvements in peptide folding would be associated with more potent endotoxin antagonism.

Methods A hybrid peptide (BU3) was generated based on combining a portion of the LPS binding domain from BPI with elements of the β-sheet domain from various chemokines. This hybrid peptide folds as a β-sheet sandwich. The ability of BU3 to (1) bind to LPS, (2) neutralize LPS, (3) kill *Pseudomonas aeruginosa* and (4) reduce serum endotoxin levels during murine

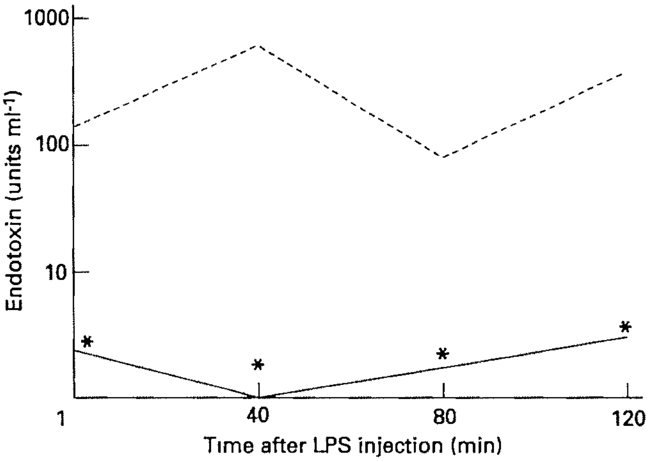

Fig. 1 *In vivo* levels of endotoxin. ----, BG16; ———, BU3. *$P<0·05$ *versus* control (Fisher's exact test)

Peptide	Endotoxin neutralization*	Bactericidal activity†
BG22	37	55
BG16	0	0
BU3	81	25

*Percentage neutralization of *Escherichia coli* endotoxin; †percentage killing of *P aeruginosa*

Wound contamination	Control group	CD4$^+$-depleted group	CD8$^+$-depleted group	CD4$^+$ and CD8$^+$-depleted group
Ultimate strength (N)				
Normal	16·9(0·58)	13·7(0·47)	20·8(0·61)	18·3(0·62)
Starch	13·1(0·5)*	14·0(0·5)	16·4(0·56)*	18·3(0·63)
Resilience (10^{-3} J)				
Normal	44·8(2·5)	25·3(1·4)	54·2(2·8)	31·5(1·8)
Starch	26·1(1·7)*	25·8(1·8)	34·0(2·2)†	32·4(2·6)
Toughness (10^{-3} J)				
Normal	157·2(5·2)	103·0(5·0)	173·9(5·8)	137·3(6·0)
Starch	92·5(5·6)*	92·7(4·3)	140·2(5·5)*	132·0(5·6)

Values are mean(s.e.m.) *$P<0\cdot05$ (paired t test)

These results demonstrate that starch causes a CD4$^+$ T lymphocyte-mediated reaction in the wound which results in impairment of wound healing demonstrated by the reduction of biomechanical parameters of the mature 10-week-old wound

Fraction of normal remaining life: a new method for defining cure in early breast cancer

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The plotting of conventional survival curves for cancer, using the interval between diagnosis and date of last follow-up or death to denote survival time, ignores the patient's expected lifespan had the patient been healthy. In human terms, the impact of a projected 10-year survival time of a woman diagnosed to have breast cancer, for example would be different for a 30-year-old patient compared with that for a 70-year-old. The authors believe that expressing outcome in terms of the fraction of normal remaining lifespan may be more meaningful They have recently described this method and wish to present its application to the data available from the Cancer Research Campaign's clinical trials.

In the new method, each patient's age at diagnosis is subtracted from the average life expectancy for that age to obtain what is called her normal remaining life (NRL) At the time of survival analysis, the percentage of NRL that has actually been lived by the patient is calculated and used in place of survival time to plot actuarial survival curves, which are called real-life expectancy curves For example, in the UK, a healthy 40-year-old woman has a normal life expectancy of 79 years and NRL of 39 years (79 minus 40 years). If at age 40 years she were diagnosed to have breast cancer, and she lived for 10 years, her survival is expressed as 26 per cent of her NRL (10/39 × 100). If she were aged 60 years at the time of diagnosis her survival would be 48 per cent (10/21 × 100) of her NRL.

To plot the real-life expectancy curves, these percentage figures were used instead of the actual number of years The mathematical and statistical procedures are exactly the same as those used in the conventional method. With this method, a node-negative woman can be said to have a 68 per cent chance of living her full NRL, which is equivalent to 'cure'. Similarly, it can be said that, overall, tamoxifen increases the chance of 'cure' from 50 to 62 per cent

The importance of the facility to express survival in terms of cure, especially for a disease such as cancer, is profound. By individualizing survival estimates according to age and expressing survival in terms of 'cure' rates, the new method makes survival estimates more meaningful, relevant and human.

Intraperitoneal hypothermia during laparoscopy enhances postoperative tumour growth

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Peritoneal insufflation with heated carbon dioxide has been shown to attenuate postoperative peritoneal inflammatory cytokine response compared with that at room temperature carbon dioxide in patients undergoing laparoscopic surgery The aim of this study was to assess the effect of gas temperature on tumour growth in an animal model.

Thirty WAG rats were randomized to undergo anaesthesia alone ($n=10$) or to be insufflated with carbon dioxide at room or body temperature ($n=20$). The rats were anaesthetized and abdominal insufflation took place at either warmed (37 ± 3°C) or normal (24°C) temperature carbon dioxide for 30 min at 6 mmHg. During insufflation, 1 ml of cultured tumour cells in suspension (1×10^5 per ml) was sprayed into the peritoneal cavity. The control group was anaesthetized as above and injected with tumour cells without insufflation. After 3 weeks the rats were killed and the extent of tumour spread assessed at autopsy using the modified Peritoneal Cancer Index (PCI), and tumour growth was compared by weighing the excised nodules.

Tumour growth in both groups that received carbon dioxide pneumoperitoneum was significantly increased compared with that in controls (control *versus* warm and cold carbon dioxide, $P<0\cdot0001$). Furthermore, there was significantly greater tumour growth in the rats insufflated with room temperature carbon dioxide compared with that in the heated carbon dioxide group (mean(s d) total tumour 0·01(0·03) *versus* 0·043(0·07) g; $P=0\cdot025$, Mann–Whitney U test). Similarly, spread as shown by the PCI scores was reduced in the warm gas group compared with the animals insufflated with cold gas (151 *versus* 266)

It is well demonstrated that postoperative tumour growth is proportional to the degree of surgical trauma. These data demonstrate that peritoneal insufflation enhances tumour growth and that a warmed pneumoperitoneal environment attenuates the growth of tumour. This effect may be mediated by reduced peritoneal trauma following insufflation with heated gas.

Expression of matrix metalloproteinases and their inhibitors in aneuryms and normal aorta

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Purpose Abdominal aortic aneurysms (AAAs) are characterized by degradation of collagen and elastin resulting from increases in matrix metalloproteinase (MMP) activity. Previous authors have identified isolated increases in the expression of specific MMPs in AAA, but none has compared relative levels of expression of particular MMPs with one another or with those of their inhibitors, the tissue inhibitors of metalloproteinases (TIMPs). This study proposed to quantify relative messenger RNA (mRNA) levels for interstitial collagenase (MMP-1), 72-kDa type IV collagenase (MMP-2), 92-kDa type IV collagenase (MMP-9), TIMP-1 and TIMP-2 in normal aorta and AAAs to provide insight as to the relative importance of each in aneurysm formation.

Methods and results Competitive polymerase chain reactions (PCRs) using gene-specific external standards and complementary DNA derived from AAAs ($n=8$, mean age 67·4 years) and normal aorta ($n=5$, mean age 40·6 years) were used to quantify mRNA levels. Results were normalized to glyceraldehyde 3-phosphate dehydrogenase (GAPDH) mRNA levels, determined via competitive PCR and compared with the Mann–Whitney U test.

were positive, and daily clinical assessment of each patient was undertaken while central venous catheters remained *in situ*.

Ninety-six catheters in 89 patients were assessed and 37 cases of CRS (39 per cent) were diagnosed (positive brush or catheter-tip culture with a positive peripheral blood culture) by conventional means. Of these, AOLC–GSLC was positive in 35 cases giving a sensitivity for the diagnosis of CRS of 95 per cent. There were four false-positive results (specificity 93 per cent). Twenty-five of the 37 cases of CRS were caused by staphlococci (13 coagulase-negative staphylococcus and 12 *Staphylococcus aureus*) and four cases were caused by group D streptococci. In eight cases a fungal septicaemia was diagnosed on the basis of AOLC–GSLC and the catheter was removed immediately and systemic antifungal therapy commenced with rapid resolution of the CRS.

In conclusion AOLC–GSLC accurately confirms potentially life-threatening CRS within 30 min and allows Gram stain and morphological characterization of the micro-organism. This enables early institution of appropriate antimicrobial chemotherapy in addition to catheter removal. The authors strongly recommend the use of AOLC–GSLC as a rapid diagnostic technique in potentially life-threatening CRS.

Hyaluronic acid induces tumour necrosis factor α production by human macrophages: implications for scarless wound healing

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Background All adult skin wounds heal by scar formation, whereas the fetus heals in a regeneration-like fashion with minimal scarring. Fetal skin is rich in the glycosaminoglycan hyaluronic acid (HA), which has been suggested to contribute to the phenomenon of scarless healing. Macrophages are essential for normal wound healing, a role facilitated by secretion of an array of cytokines. Of these, tumour necrosis factor (TNF) α has been shown to reduce wound collagen levels and thus scarring. This study examined the ability of HA to stimulate TNF-α production by human macrophages.

Methods The human U937 myelomonocytic cell line was differentiated into DU937 adherent macrophages. Macrophage monolayers were exposed to HA at concentrations of 100, 10, 1 and 0·1 μg ml^{-1} for 24 h to allow for cytokine production. Macrophage-conditioned media were then harvested and assayed for TNF-α content using a standard L929 fibroblast bioassay. The cytotoxicity (and therefore TNF-α content) of each supernatant was compared with that of a control and expressed as percentage cytotoxicity.

Results Exposure of macrophages to HA significantly stimulated TNF-α production when present at concentrations of 100 and 10 μg ml^{-1} within the culture system. This was demonstrated by percentage cytotoxicity, expressed as median (interquartile range), of 77·5 (67–85) per cent ($P = 0{\cdot}029$, Mann–Whitney *U* test) and 33·5 (29–34·5) per cent ($P = 0{\cdot}03$) respectively. This effect was associated specifically with TNF-α generated during HA exposure, as the cytotoxic effects of these media could be virtually abolished by addition of anti-TNF-α antibody, reducing cytotoxicity to 8·5 (7–10) and 9 (8–10) per cent respectively ($P < 0{\cdot}01$)

Conclusion These observations indicate that HA stimulates TNF-α production by human macrophages. It is known that TNF-α can downregulate fibroplastic collagen synthesis within experimental wounds. It is suggested that high levels of HA within fetal wounds may play a part in limiting fibroplasia, and thereby limit scarring, via an upregulation of TNF-α production from wound macrophages

New assessment tool: the Patient Assessment and Management Examination

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Background The major goal of certification is to assure the public that the candidate is competent in all facets required of the position. An evaluation system that is reliable and valid is essential. Traditional techniques, such as the in-training evaluation (ITER) and oral examinations (OEs), suffer from poor reliability. Furthermore, all components of clinical competence, such as the ability to discuss management plans and interact effectively with patients, are not assessed. Thus, the Patient Assessment and Management Examination (PAME) was developed, with the aim of better assessment of the skills required by the specialist

Method A six-station standardized patient-based evaluation was developed. Each station was 30 min long and consisted of four components: an initial history and physical examination, ordering and interpretation of investigations, a patient follow-up and, finally, a structured oral examination. Patients were trained to modulate responses based on the candidate's approach. Stations were scored using global ratings by general surgeons on a five-point scale (3, competent for independent practice). The PAME results were compared with the last two ITERs, the clinical knowledge component of the ITERs (ITER-CK) and an in-house OE.

Results Eighteen senior general surgery residents in their fourth or fifth year of clinical training participated. The overall reliability of the examination was 0·70 (Cronbach's α). Residents in their last 6 months of training scored significantly better than those with more than 6 months of training left to complete ($t = 3{\cdot}06$, $P = 0{\cdot}007$), demonstrating evidence of construct validity. The ITER, ITER-CK and OE showed no evidence of construct validity, with the first two showing a test–test reliability of less than zero. Pearson product moment correlations between the PAME and each of the other measures were: ITER 0·24, ITER-CK 0·38 and OE 0·13. The poor correlations are probably due to the poor reliability of the traditional measures and the different skills being assessed

Conclusion The PAME had better psychometric properties than other measures of clinical competence and was able to provide an assessment of many areas that are currently not evaluated formally. This type of test may be appropriate for certification decisions.

T cell-dependent mechanism of starch impairment of wound healing

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It has been shown previously that starch containing glove powder interferes with wound healing in an immunocompetent but not in a congenitally T cell-depleted nude rat.

Some 128 thymectomized PVG rats were assigned randomly to four groups and depleted of CD4$^+$, CD8$^+$, or CD4$^+$ and CD8$^+$ lymphocytes with monoclonal antibodies. Bilateral paramedian abdominal incisions were carried out under general anaesthesia and closed with mass closure technique with a continuous 3/0 monofilament suture, and the skin closed separately with a 5/0 monofilament suture. Starch (0·5 ml of a suspension 100 mg ml^{-1}) was instilled under one randomly selected wound. Wounds were harvested at 10 weeks and examined by tensionometry to give values of ultimate strength, resilience (energy absorbed to the elastic limit) and toughness (total energy absorbed before rupture).

Starch decreased the ultimate strength, resilience and toughness of wounds of rats either not depleted or depleted of CD8$^+$ lymphocytes only. Depletion of CD4$^+$ lymphocytes abolished the response of starch-impairing wound healing.

clinicians provides a valid measure of clinical opinion, but is impractical for research use. The authors aimed to develop a new method for evaluating surgical emergency admissions and to compare it with two standard methods, the Appropriateness Evaluation Protocol (AEP) and the Oxford Bed Study Index (OBSI).

Some 250 surgical emergency cases were studied prospectively. An index was derived by stepwise logistic regression on social, clinical and organizational factors to seek associations with the verdict of a consensus panel. The index was compared with the panel verdict, the AEP and the OBSI in these cases and in a further 50 patients.

The AEP and OBSI were sensitive (96–100 per cent) but not specific (13 per cent) predictors of the panel's decision. The Aintree Index gave comparable sensitivity (92–100 per cent) with better specificity (20–22 per cent) at low scores, and specificity of up to 89 per cent at high scores. The odds in favour of being classified as justified were 5.1 for patients with an Aintree Index of 4 or more.

The AEP and OBSI have poor specificity for justified emergency surgical admissions. The Aintree Index provides a more flexible measure of justifiability, which agrees better with the decision of a consensus clinical panel.

Mucosal immune cell and enterocyte activation in malnourished surgical patients

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Malnourished patients have a high incidence of postoperative sepsis and there is increasing evidence that altered host gastrointestinal defence plays a central role in the development of this syndrome. It has recently been shown that intestinal permeability is increased in malnourished patients but the mechanism underlying gut barrier compromise is unclear. This study examined lamina propria lymphocyte and enterocyte function, key components of gastrointestinal defence, in malnourished surgical patients.

Twenty-three patients were studied, 11 with protein-calorie malnutrition, defined by subjective global assessment and serum albumin concentration (median $35\,\text{g l}^{-1}$), and 12 well nourished disease-matched controls. Endoscopic duodenal biopsies were stained for immunological features and scored blindly from 0 to 4 by a pathologist. The polymerase chain reactino was used to determine mucosal expression of the activation marker human leucocyte antigen (HLA)DR, the proinflammatory cytokine tumour necrosis factor (TNF) α and the anti-inflammatory cytokine interleukin (IL) 10. Results are expressed as the ratio of gene product to a coamplified housekeeping gene. The results (median and interquartile range) were as shown in the *Table*

	Controls	Malnourished
Mucosal immunohistochemistry score		
CD3 (pan T cell)	2 (1–2)	3 (2–3)*
CD68 (macrophages)	2 (2–2)	3 (3–3)*
HLA-DR (lamina propria lymphocytes)	3 (2–3)	3 (3–3)*
HLA-DR (enterocytes)	0 (0–1)	3 (3–3)*
Mucosal gene expression		
HLA-DR	0·8 (0·6–1·0)	1·0 (0·9–1·0)*
TNF-α	0·1 (0–0·4)	0·2 (0–0·6)
IL-10	0·7 (0·6–1·1)	0·4 (0–0·7)*

*$P < 0{\cdot}05$ (Mann–Whitney *U* test)

These data provide phenotypic and molecular evidence of intestinal mucosal immune cell and enterocyte activation in malnourished patients. This was associated with reduced expression of the anti-inflammatory cytokine IL-10. This suggests a mechanism that may have relevance to the increased intestinal permeability and increased risk of sepsis in the malnourished patient.

Extraperitoneal bupivacaine in laparoscopic day-care inguinal hernia repair: a randomized trial

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Totally extraperitoneal (TEP) laparoscopic inguinal hernia repair is gaining popularity and the authors' preference is to perform this procedure as a day case. In a randomized controlled trial, the efficacy of extraperitoneal bupivacaine for postoperative analgesia in day-care TEP repair was evaluated.

Fifty-four consecutive patients undergoing TEP repair through the day ward were randomized to receive an intraoperative infusion into the extraperitoneal space of either 40 ml of 0·25 per cent bupivacaine with adrenaline (bupivacaine group, $n = 28$) or 40 ml of normal saline (control group, $n = 26$). All other factors were standardized including surgical and anaesthetic technique and analgesic medication. patients were assessed blindly after operation, on discharge from hospital, and at 24 h, 1 week and 1 month.

Compared with controls, patients treated with bupivacaine had lower median (range) visual analogue pain scores on discharge (1·5 (0–5·9) *versus* 3·7 (0·2–6·9), $P = 0{\cdot}03$) and were more frequently pain free (54 *versus* 31 per cent, $P = 0{\cdot}8$). Although this difference had gone by 24 h the bupivicaine group continued to recover faster, stopping analgesia earlier (2 (0–7) *versus* 3 (0–21) days, $P = 0{\cdot}01$) and returning to full activity earlier (2·5 (1–14) *versus* 5 (1–21) days, $P = 0{\cdot}01$). Of the patients receiving bupivacaine, 100 per cent were completely satisfied with the procedure compared with 81 per cent in the control group ($P = 0{\cdot}02$).

Extraperitoneal bupivacaine minimizes postoperative pain and facilitates recovery in the days following TEP repair, increasing patient satisfaction. The lasting benefits beyond the period of action of bupivicaine may reflect improved patient confidence through minimization of discomfort in the early postoperative period.

Rapid qualitative technique for the *in situ* diagnosis of catheter-related sepsis

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Acridine orange leucocyte cytospin (AOLC) and Gram stain leucocyte cytospin (GSLC) have proven benefits in the rapid diagnosis of both bacteraemic and fungicaemic episodes in paediatric practice. In adults, these diagnostic methods are not used routinely as peripheral blood microbiological counts are markedly lower than in paediatric patients. Catheter-related sepsis (CRS) is associated with significantly raised catheter blood microbiological counts compared with peripheral blood counts, and therefore the AOLC–GLSC technique performed on through-catheter samples of blood can provide an accurate and rapid (30-min) diagnosis of CRS without the need for catheter removal.

Catheter samples of blood were taken in 96 episodes of suspected CRS and the AOLC–GSLC technique was performed to detect the presence of micro-organisms. For comparative assessment, endoluminal brushing, catheter-tip culture (upon catheter removal) and peripheral blood cultures were taken, according to the authors' conventional protocol. Catheters were left *in situ* unless AOLC–GSLC or subsequent brush cultures calcium channel antagonist) in modulating resting tone and agonist-induced contractions in porcine internal anal sphincter (IAS) and circular muscle of the rectum. Porcine tissue has similar properties to human and provides a good model to study the effects of pharmacological manipulation.

Smooth muscle strips from the IAS and rectal circular muscle of eight large white pigs were mounted for isometric tension recording in a superperfusion organ bath. Strips were constantly perfused with Krebs solution The effects of noradrenaline 10^{-7}–10^{-4} mol l^{-1} and carbachol 10^{-7}–3×10^{-4} mol l^{-1} were assessed in normal Krebs, calcium-free solution with EGTA (chelating agent) and in the presence of nifedipine 10^{-6} mol l^{-1}.

IAS strips ($n = 18$) developed tone and spontaneous activity Noradrenaline produced dose-dependent contractions. In calcium-free Krebs, which also drains internal calcium stores, tone and activity were abolished and no contractions were elicited in response to noradrenaline Tone, activity and normal contractions returned on reperfusion with Krebs. Nifedipine also abolished tone and spontaneous activity but contractions to noradrenaline were only slightly attenuated (maximum response 70 per cent of control, $P < 0{\cdot}01$).

In contrast, rectal smooth muscle strips ($n = 24$) developed spontaneous activity but no resting tone and contracted in response to carbachol. In calcium-free Krebs the spontaneous activity and carbachol contractions were abolished but returned when calcium was reintroduced to the perfusate. Addition of nifedipine to the perfusate abolished spontaneous activity and markedly reduced contractions (maximum response less than 20 per cent of control, $P < 0{\cdot}001$).

These data suggest that spontaneous activity and resting tone are dependent upon extracellular calcium and flux across the cells. Agonist-induced contraction in the IAS is likely to be due mainly to the release of intracellular stores whereas rectal circular smooth muscle depends mainly on extracellular calcium entering the cell for contraction. The attenuation of contractions in both tissues and the abolition of resting tone in the IAS suggests that nifedipine may be useful in the management of patients with anorectal disorders.

Anti-interleukin 10 antibody restores burn-induced defects in T cell function

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Background The authors' previous studies have shown that susceptibility to sepsis following severe injury correlates with reduced production of T helper 1 cytokines (interleukin (IL) 2 and interferon (IFN) γ) and a persistence of T helper 2 cytokines (IL-4 and IL-10). The mechanisms responsible for this effect are not clear. We now report use of a T-dependent antigen to study the effect of burn injury on antigen-specific T helper cell functions *in vivo* and the effect of anti-IL-10 antibody (IL-10ab) on these functions.

Methods Male A/J mice were anaesthetized and given a 25 per cent scald burn or sham burn On day 0 all mice were immunized subcutaneously with 100 μg TNP-haptenated ovalbumin (TNP-OVA) in complete Freund's adjuvant. Mice (ten per group) were given 250 μg monoclonal rat antimurine IL-10ab or control rat immunoglobulin (Ig)G on day 0 and 100 μg IL-10ab or IgG on day 2 On day 10 mice were killed to obtain serum and spleen cells. TNP-specific serum antibody titres were determined by enzyme-linked immunosorbent assay (ELISA). Splenic T cell proliferation and cytokine production in response to TNP-OVA or to anti-CD3 antibody were determined by [3H]thymidine incorporation and enzyme-linked immunosorbent assay respectively.

Results Burn injury resulted in depressed levels of the TNP-specific IgG2a antibody isotype (T helper 1 dependent) whereas TNP-specific IgG1, and IgE (T helper 2 dependent) and IgM isotype levels were similar in sham and burnt mice. IL-10ab but not IgG significantly restored and IgG2a response.

Treatment groups	[^{3}H]Thymidine (c p.m.) TNP-OVA	[^{3}H]Thymidine (c p.m.) Anti-CD3	IL-2 (units ml^{-1}) TNP-OVA	IFN-γ (units ml^{-1}) TNP-OVA
Sham + IgG	18238(597)	11701(129)	18·2(0·6)	48(4·2)
Sham + IL-10ab	23362(498)	16609(312)	49·2(3·5)	114(0·7)
Burn + IgG	9451(86)*	12751(496)	6·1(0·1)*	0*
Burn + IL-10ab	19722(436)	17020(398)	40(1·2)	332(10)

Values are mean(s.e.). *$P < 0{\cdot}01$ *versus* sham + IgG (Student's *t* test)

Burn injury reduced antigen-specific proliferation whereas anti-CD3 proliferation was normal IL-10ab restored antigen-specific proliferation whereas anti-CD3 proliferation was normal. IL-10ab restored antigen-specific proliferation as well as antigen-specific IL-2 and IFN-γ production.

Conclusion It is concluded that (1) burn injury induces a loss of antigen-specific T helper 1 cell function and (2) IL-10 acts as a trigger to downregulate T helper 1 cell function after injury.

Loss of endothelial barrier function requires neutrophil adhesion

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The inflammatory response is characterized by cytokine-induced upregulation of endothelial adhesion molecules followed by polymorphonuclear neutrophil (PMN) adhesion and breakdown of tight junctions between cells. The purpose of this investigation was to determine whether PMN adhesion is an essential element in the alteration of endothelial permeability or whether cytokines alone can produce this change.

Human umbilical vein endothelial cells (ECs) were exposed to formyl-methionyl-leucyl-phenylalanine activated PMNs. In a second series of experiments, PMNs were contained in a microporous membrane which allowed passage of secreted cytokines but not cells. Permeability was quantified using trans-endothelial electrical resistance (TEER; ohm cm^2), and the expression of two cell adhesion molecules, endothelial leucocyte adhesion molecule (ELAM) 1 and intercellular adhesion molecule (ICAM) 1, was measured by flow cytometry (percentage shift). Cytokine production was monitored by enzyme-linked immunosorbant assay (pg ml^{-1}).

Stimulated PMNs secreted comparable amounts of cytokines whether allowed access to ECs or trapped in a microporous membrane (mean(s.d.) interleukin 1α 5·88(2·38) *versus* 3·65(1·84) pg ml^{-1}, tumour necrosis factor α 10·27(3·21) *versus* 6·61(1·82) pg ml^{-1}. Upregulation of ELAM-1 and ICAM-1 was observed whether PMNs were free or restricted (mean(s.d.) 52·97(2·14) *versus* 75·32(4·19) and 71·66(7·37) *versus* 73·66(4·32) per cent respectively). TEER was unchanged in controls (no PMNs) and when PMNs were membrane restricted In contrast, TEER decreased precipitously (from 100 to 61 per cent, $P < 0{\cdot}05$) if PMNs were allowed access to ECs.

Cytokine secretion by PMNs is independent of EC contact and is sufficient to upregulate adhesion molecules However, PMN adhesion is essential for the critical loss of endothelial barrier function which leads to diapedesis of activated PMNs and eventual tissue injury.

Evaluation of surgical emergency admissions: a comparison of three methods

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The percentage of surgical emergency admissions that are clinically justified is controversial. A panel of experienced cytokeratin 18 (CK-18) and $2{\cdot}5\times10^4$ events observed by flow cytometry. The remaining sample was incubated with Ber-EP4-coated magnetic beads for 1 h, and beads and adherent cells subjected to RT-PCR using CEA primers. Results are expressed as the lowest number of detectable cells per ml of blood.

	COLO 320	LoVo	SW480	SW948
Optimal primary antibody	None	Ber-EP4	Ber-EP4	Ber-EP4
Immunocytochemistry	Negative	10^3	10^3	10^3
CK-18 flow cytometry	Negative	$>10^6$	10^4	10^3
CEA RT-PCR	Negative	10^3	Negative	10^5

Bone marrow was obtained from 13 consenting patients undergoing surgery for colorectal cancer, and from four controls undergoing colonic surgery for benign disease. Aspirates (5 ml) from both posterior iliac crests were obtained and examined as above. Micrometastases were detected more frequently using immunocytochemistry (seven of 13), than flow cytometry (three of 13) or RT–PCR (none of 13). Samples from control cases were negative using all methods.

Results from the three informative cell lines examined and patient data suggest that flow cytometry and RT–PCR may be inferior to immunocytochemistry in the assessment of minimal residual disease following surgery for colorectal cancer.

Detection of replication error in colorectal cancer: a non-radioactive, single marker technique

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Microsatellite instability (MIN), implying a replication error phenotype (RER$^+$), characterizes a proportion of colorectal cancers. Generally, the polymerase chain reaction (PCR) using several markers may be required and debate remains as to how many positive results are needed to infer RER positivity. Minisatellite variant repeat units (MVRs) are long DNA sequences which show extreme levels of allelic variability, not only in repeat copy number but also the interspersion pattern. MVR mapping by PCR (MVR-PCR) assays the interspersion pattern of variant repeat units along minisatellite alleles. The authors have designed a novel set of MVR–PCR primers specific to two MVR loci (MS31A and MS32) and simplified their detection to non-radioactive PCR.

Analysis of 32 colorectal tumour–normal pairs using MVR–PCR was compared with that using ten microsatellite markers. Four patients showed MIN with three or more of the microsatellite markers suggesting a RER$^+$ phenotype. All three were positive by MVR–PCR. Three patients showed a RER$^+$ phenotype by MVR–PCR which was not observed with any of the microsatellite markers and in two of these mutations in a DNA mismatch repair gene (*hMLH1*) have been identified.

These results suggest that MVR–PCR may be an alternative, simpler method of detecting RER$^+$ phenotype.

Serum vascular endothelial growth factor can be used to predict oncological clearance following colorectal cancer surgery

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Vascular endothelial growth factor (VEGF) is a potent angiogenic cytokine essential for the growth and dissemination of solid tumours and its level is raised in the serum of patients with colorectal cancer. This study aimed to determine if serum VEGF could be used to predict oncological clearance of colorectal cancer following surgery.

Some 63 patients with colorectal cancer were recruited: 50 had curative resection and 13 with liver metastasis had palliative resection. Eleven patients underwent resection for benign conditions. Blood samples were taken before and 4–6 h after operation and serum stored at −80°C until assay for VEGF 165 by enzyme-linked immunosorbent assay. All patients had 3- and 6-monthly follow-up magnetic resonance imaging scans. Analysis was done by Mann–Whitney and *t* tests.

Postoperative VEGF (median interquartile range 195·3(116·3–522·0) pg ml^{-1}) showed a significant fall in the curative resection group from preoperative VEGF levels (568·6(302·4–868·8) pg ml^{-1}) ($P<0{\cdot}0005$). These postoperative levels were comparable to VEGF levels in 136 normal controls (173·8(92·5–282·3) pg ml^{-1}) ($P=0{\cdot}06$). There was no significant change in the group with systemic disease (preoperative VEGF 701·3(614·3–948·6) pg ml^{-1}; postoperative VEGF 690(529·7–1169·3) pg ml^{-1}; $P=0{\cdot}52$). Postoperative VEGF (387·7(172·4–968·5) pg ml^{-1}) following benign resection showed no significant difference from preoperative levels (270·4(153·1–797·9) pg ml^{-1}) ($P=0{\cdot}42$).

Primary colorectal cancer and metastases result in an increase in serum VEGF. Removal of primary tumour should mitigate the high levels unless overt or occult metastatic disease exists as shown by this study. It is concluded that serum VEGF can be a useful took to predict curative colorectal resections.

Production and secretion of endothelin 1 in colorectal cancer

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Endothelin 1 (ET-1) is a vasoactive peptide secreted by endothelial cells and other cell types. It has a wide range of physiological and pathophysiological effects, e.g. enhancement of cellular growth and angiogenesis. ET-1 is produced by many cancer cell lines and acts in an autocrine/paracrine fashion.

To investigate the production of ET-1 in colorectal cancer, ET-1 plasma levels were measured by radioimmunoassay in patients with primary colorectal cancer ($n=34$), patients with colorectal cancer and liver metastases ($n=26$), and age- and sex-matched controls ($n=21$). Patients with conditions which raise ET-1 plasma levels were excluded. Mean(s.d.) ET-1 levels were significantly raised in patients with colorectal cancer (4·3(1·3); $P<0{\cdot}01$) and metastases (4·4(1·6); $P=0{\cdot}01$) compared with controls (2·8(1·3)). No significant difference was seen between patients with and without liver metastases. Furthermore, colorectal cancer and normal colon frozen specimens from surgical patients ($n=26$) were stained immunohistochemically for ET-1. ET-1 was only expressed in the apical cell layer of the mucosa and blood vessels of normal colon. In tumour, ET-1 was strongly expressed in the cytoplasm of malignant cells, the stroma and blood vessels.

ET-1 production and secretion suggests its involvement as a mitogenic/angiogenic factor in colorectal cancer

Effects of nifedipine in the rectum and internal anal sphincter

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Glyceryl trinitrate has been shown to reduce resting anal pressure and aid healing of anal fissures. However, some patients develop tachyphylaxis and the fissure fails to heal. The purpose of this study was to assess the effects of nifedipine (an L-type

Glutathione S-transferase theta family messenger RNA expression in human colorectal cancer

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The glutathione S-transferases (GSTs) are a superfamily of enzymes which consists of four main subclasses, alpha, mu, pi and theta. GSTs play significant roles in the detoxification of mutagens and chemotherapeutic agents and have been associated with multiple drug resistance Messenger RNA (mRNA) expression of the two members of the GST theta family, GSTT1 and GSTT2, has been analysed in 25 matched colorectal tumour/mucosa pairs.

Total cellular RNA was extracted from matched colorectal mucosa and tumour pairs and subjected to reverse transcription (RT) using an oligo dT primer. RT–polymerase chain reaction (PCR) was performed using specific oligonucleotide primers to detect GSTT1, GSTT2 and β-actin (a ubiquitously expressed gene). The PCR products were analysed by polyacrylamide gel electrophoresis and visualized by ethidium bromide staining under ultraviolet transillumination. The specificity of the PCR products was confirmed by sequencing.

GSTT1 mRNA was expressed in 20 of 25 samples of mucosa and 22 of 25 tumour samples, and GSTT2 mRNA in 13 of 25 mucosa samples and 21 of 25 tumour samples An increased level of expression of GSTT2, but not GSTT1, was observed in tumour samples ($P = 0·004$ and $P = 0·184$ respectively, Wilcoxon matched pair signed ranked test). This suggests that GSTT2 may be important in inherent resistance of colorectal tumours to chemotherapy.

Abnormal expression of β-catenin predicts poor survival in patients with colorectal carcinoma

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The E-cadherin–catenin cell adhesion complex is responsible for maintenance of the normal epithelial phenotype. Abnormalities of this complex, which includes E-cadherin, α-catenin and β-catenin, result in reduced cell–cell adhesion which is critical both in tumour development and metastasis. The cytoplasmic protein β-catenin is the key regulator of the complex and is also involved in signalling pathways controlling cell growth and differentiation This study was done to determine if changes in expression of β-catenin in colorectal cancer tissue might serve as a prognostic indicator.

Tumour specimens from 60 patients with colorectal adenocarcinoma were examined for expression of β-catenin using routine immunohistochemical techniques and Western blot analysis. Patients with tumours displaying weak or absent membranous expression of β-catenin ($n = 35$, $P = 0·003$, log rank test) or widespread nuclear expression of β-catenin ($n = 11$, $P = 0·002$) had worse survival, independent of both Dukes stage and tumour grade, compared with those with normal expression.

Loss of membranous expression of β-catenin is likely to reflect defects in cell–cell adhesion, and overexpression of β-catenin within the nucleus may be related to unregulated signalling events. These changes may result in a greater propensity for individual cells to metastasize and thus serve as a marker for patients most at risk of developing recurrent colorectal cancer.

Vasoconstrictors improve delivery of hepatic arterial 5-fluorouracil in a model of colorectal liver metastases

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Blood vessels in colorectal liver metastases lack innervation and smooth muscle Hence regional chemotherapy might be improved by the co-administration of vasoconstrictors.

Liver tumours were established by intraportal injection of MC28 syngeneic tumour cells in hooded Lister rats. Fourteen days after inoculation the gastroduodenal artery was cannulated and saline, angiotensin II, endothelin-1, L-NAME, noradrenaline or vasopressin ($n = 6$ per group) were infused with [^{3}H]-5-fluorouracil (^{3}H5FU) over 30 min. Tumours and liver from the same lobe were removed, solubilized and radiocounted

None of the agents produced a significant change in ^{3}H5FU uptake compared with the saline group in the normal liver. The ^{3}H5FU uptake in the tumour was as follows (mean(s d.) c p.m. $g^{-1} \times 10^5$): saline 5·1(3·2), angiotensin 5·1(1·4), endothelin-1 15·8(14·2), L-NAME 3·5(1·3), noradrenaline 19·1(9·8) and vasopressin 6·8(3·5). Noradrenaline was the only agent to produce a significant increase in ^{3}H5FU tumour uptake ($P < 0·01$)

Noradrenaline may be used to improve drug delivery in hepatic arterial chemotherapy for colorectal liver metastases.

Effects of local hypothermia on anal canal pressures in patients without anal canal disease

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Cooling of the anal and perianal region as a treatment for painful anal canal conditions has been recommended for many years. but little information exists on its effects. This study investigated the effect of local anal canal hypothermia on resting anal canal pressure (RACP) and maximal squeeze pressure (MSP)

Nine patients without anal canal disease were studied before and after anal canal hypothermia had been induced by the introduction of a frozen, water-filled rubber glove finger for 10 min. Similar data were obtained in four of these patients after insertion of a thin rubber glove-covered non-frozen proctoscope of similar size to the frozen finger.

The mean(s.d.) anal canal temperature decreased significantly from 37·1(0·2) to 34·6(0·6)°C ($P < 0·001$, paired *t* test) Mean(s.d.) RACP was significantly reduced from 66·7(12·2) to 49·4(18·3) cmH$_2$O ($P < 0·01$); mean(s d.) time to recovery of prehypothermia RACP was 30·4(13·3) min. There was no significant change in RACP (73·8(12·5) *versus* 72·5(16·6) cmH$_2$O) after insertion of the non-frozen proctoscope. Mean(s.d) MSPs of 238·3(20·4) and 230·8(24·8) cmH$_2$O before and after induction of hypothermia were similar

This study demonstrates that local anal hypothermia reduces internal sphincter pressure without affecting the external sphincter. This provides a rationale for its use in treatment of conditions where internal sphincter pressures are high.

Assessment of minimal residual disease following surgery for colorectal cancer

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The use of flow cytometry and reverse transcriptase–polymerase chain reaction (RT-PCR) to detect very small numbers of tumour cells in a large excess of normal cells has been described recently with potential application to the assessment of minimal residual disease following surgery for colorectal cancer. This investigation formally compares the sensitivity of these methods with standard immunocytochemistry.

Four colorectal cancer cell lines (Colo 320, LoVo, SW480, SW948) were stained with monoclonal antibody to each of three antigens present in colorectal epithelia (carcinoembryonic antigen (CEA), MNF and Ber-EP4) to determine the optimal primary antibody and used to 'spike' 5 ml of blood at concentrations of 10^6, 10^5, 10^4, 10^3 and 10^2 per ml. Following Ficoll separation, cytospin slides were prepared from the mononuclear layer at 5×10^4 cells per slide and stained using the optimal primary antibody as established above. Some 1×10^5 cells were labelled with an FITC-conjugated mouse antihuman risk of seeding of tumour cells by CO_2 is markedly lower ($1:10^4$, (11 d.f., $P<0·001$, Kruskal–Wallis) than the risk of mechanical inoculation by the instruments These results suggest that, in most cases, port-site metastases might be preventable, if mechanical contamination of the port sites can be avoided.

Co-culture of human fibroblast and colonic cancer cell line upregulates expression of fibroblast-derived matrix metalloproteinase (MMP) 2 and MMP-9

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Background Matrix metalloproteinases (MMPs) are capable of degrading extracellular matrix and have been implicated in tumour invasion. The stromal cells of the tumour, mainly fibroblasts, are the principal cells elaborating the MMPs. The interaction between colonic cancer cells and fibroblasts which leads to increased MMP expression is not well understood. This issue was addressed by co-culturing human colonic cancer cells and fibroblasts.

Methods The fibroblast cell lines KB16F and DB12F and colonic cancer cell lines HT115 (highly invasive) and HRT18 (less invasive) were grown in separate flasks. Some $0·6 \times 10^6$ tumour cells were added and to each fibroblast cell type incubated for 24 h. The medium was removed and cells were washed three times with serum-free medium Then 5 ml DMEM with 0·2 per cent lact albumine hydrolysade was added to each flask which was then incubated for a further 48 h. In a subsequent experiment, the conditioned medium from the cancer cell line was added to the fibroblast cell line and cells incubated for a similar duration The medium was removed from each flask at 24 and 72 h of the experiment and subjected to standard sodium dodecyl sulphate–polyacrylamide gel electrophoresis gelatin zymography. The lytic bands were sized against standard markers, and MMP-2 and MMP-9 identified. The zymograms were scanned using a laser densitometer and quantitated using computer-aided analysis.

Results The fibroblast cell line constitutively expressed pro-MMP-2 and active MMP-2 while the colonic cancer cell line did not produce any MMP. There was a 1·5-fold increase in the ratio of active MMP-2 to total MMP-2 secreted from fibroblasts both when co-cultured with the cancer cell line and also when exposed to its conditioned medium. MMP-9 expression increased ninefold and was evident only when the cells were co-cultured

Conclusion These data suggest that (1) colonic cancer cells upregulate expression of fibroblast-derived MMP-2 and MMP-9; (2) increased activation of MMP-2 results from substances liberated by cancer cells, and (3) MMP-9 expression results mainly from cell–cell contact and/or a cancer cell membrane component.

Expression of parathyroid hormone-related protein in prostate cancer

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Bone metastases occur commonly from carcinoma of the prostate and breast but metastases from prostatic adenocarcinoma are predominantly sclerotic whilst those from breast are osteolytic Bone metastasis from breast cancer occurs as a result of production of parathyroid hormone-related protein (PTHrP), a potent lytic factor, by both primary and metastatic cancer with overexpression of the PTHrP receptor in bone metastases

To determine the role of PTHrP and its receptor in the development of bone metastases from prostate adenocarcinoma archival samples of benign prostatic hyperplasia (BPH), carcinoma and bone metastases were examined for messenger RNA (mRNA) to PTHrP receptor using *in situ* hybridization and for production of PTHrP protein by immunochemistry Slides were scored using the product of intensity of signal or stain and the number of positive cells (1, fewer than 20 per cent; 2, 20–80 per cent, 3, more than 80 per cent).

		PTHrP receptor mRNA				PTHrP 1–34 protein			
	Total no	High	Normal	Low	Median score	High	Normal	Low	Median score
BPH	18	2	10	6	2 (0–6)	3	12	3	3 (0–6)
Carcinoma	22	0	4	18	0 (0–3)	10	10	0	3 (2–9)
Bone metastases	8	3	2	3	3 (0–6)	2	2	4	0 (0–6)

PTHrP protein expression was increased in malignant tumours compared with that in BPH but expression was reduced in bone metastases ($P=0·003$, Fisher's extact test). PTHrP receptor expression was absent in primary malignancies ($P<0·01$, χ^2 test) but overexpressed in bone metastases Increased PTHrP receptor may lead to survival of tumour cells in bone but the reduced expression of PTHrP protein may explain why sclerotic metastases predominate in prostate cancer.

Effect of the cell cycle of aminolaevulinic acid-induced phototoxicity *in vitro*

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Aminolaevulinic acid (ALA) induces cellular generation of protoporphyrin IX (PpIX), a photosensitizer used in photodynamic therapy (PDT) Cellular sensitivity to PDT will depend on the intracellular levels of PpIX and the intrinsic sensitivity of the cell to damage by reactive oxygen species In a population of tumour cells, cells will exist in all phases of the cell cycle. Metabolic differences are known to exist between the phases of the cell cycle which may affect their ability to generate PpIX Differential sensitivity to free radical toxicity occurs between phases of the cell cycle, with G2 and S phase cells being most sensitive to radiotherapy The aim of this study was to determine if PDT cytotoxicity is also sensitive to cell-cycle variation

Human bladder cancer cells (HT1197) were synchronized using a double thymidine block technique. PDT-induced cytotoxicity was determined by incubating synchronized cells in each phase of the cell cycle with ALA 1 mmol l^{-1} for 1 h and treating them with an LD_{50} or LD_{80} light dose. A colorimetric cytotoxicity assay (using tetrazolium bromide) was performed and percentage cell survival calculated

	Survival (%)	
Cell cycle phase	LD_{50}	LD_{80}
S	50·8 (32·4–65·2)*	24·8 (17–29·5)
G_2	47·1 (32·9–48·2)*	19·1 (17–21·6)*
G_1	67·7 (53·8–102)	25·7 (15·7–39)

Values are median (range) *$P<0·05$ *versus* G_1 (Mann–Whitney *U* test)

At LD_{50} cells in G1 are less sensitive to photodynamic therapy than cells in G2 and S phases whereas at LD_{80} G2 cells were most sensitive This difference may reflect greater sensitivity of G2 and S phase cells to singlet oxygen damage or different rates of cellular PpIX synthesis during ALA exposure between cell-cycle phases These differences may be of relevance as heterogeneity of response may facilitate tumour recurrence after clinical PDT lymph nodes which should include immunohistochemical examination. Thus patients with a minimal residual tumour load who might benefit from an adjuvant therapy could be selected.

Effect of hypoxia on aminolaevulinic acid-induced cellular phototoxicity *in vitro*

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Aminolaevulinic acid (ALA) induces cellular generation of the photosensitizer protoporphyrin IX (PpIX) via the haem biosynthetic pathway. PpIX is used as a sensitizer for photodynamic therapy (PDT). Several of the steps in the synthesis of PpIX are thought to be oxygen dependent, as is PDT toxicity which is mediated by singlet oxygen. Tumours are known to have heterogeneous oxygen saturations (tumour 0–5 per cent oxygen, normal 5–10 per cent, *in vitro* 21 per cent). The aim of this study was to determine whether PpIX synthesis and PpIX-mediated PDT are oxygen dependent.

Human bladder cancer cells (HT1197) were incubated with ALA 1 mmol l^{-1} for 4 h under varying oxygen tensions (0–21 per cent). PpIX (ng per μg protein) was estimated by spectrofluorimetry. PDT-induced cytotoxicity was determined by incubating HT1197 cells with ALA 1 mmol l^{-1} for 4 h under varying oxygen tensions followed by irradiation with 1 J cm^{-2} violet light. A colorimetric cytotoxicity assay (using tetrazolium bromide (MTT)) was performed and percentage cell survival calculated.

	Oxygen tension (%)				
	0	2·5	5	10	21
Total PpIX (ng per μg protein)	0·14 (0·08–0·28)*	0·28 (0·1–0·44)*	0·34 (0·2–0·72)*	1·05 (0·3–3·2)	0·68 (0·4–1·2)
Cellular PpIX (ng) per μg protein)	0·06 (0·03–0·09)*	0·16 (0·1–0·2)*	0·15 (0·13–0·3)	0·24 (0·1–1·7)	0·21 (0·1–0·25)
Survival (%)	82 (43–106)*	67 (58–73)*	48 (39–57)*	45 (27–56)	35 (21–51)

Values are median (range) $^*P < 0{\cdot}05$ *versus* at 21 per cent oxygen (Mann–Whitney *U* test)

Hypoxic cells, such as are found within the tumour microenvironment, produce less PpIX than normoxic cells. Sensitivity to PDT is also reduced. This suggests that hypoxic areas of tumour may be resistant to ALA-induced PDT, possibly because of reduced singlet oxygen production and/or reduced photosensitizer generation.

Somatic mutations and allelic loss at *APC* in desmoids

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Background Germline mutations of the *APC* gene on chromosome 5q22 are responsible for familial adenomatous polyposis (FAP), an autosomal inherited condition characterized by the development of multiple colorectal adenomas in adolescence. Desmoids are an uncommon but clinically important extracolonic manifestation of FAP. It has been suggested that desmoid formation is consequent upon functional loss of both alleles of the *APC* gene: one allele inactivated by the germline mutation and the second by somatic mutation or microdeletion (manifest as loss of heterozygosity; LOH).

Methods Nine desmoids (from seven patients with FAP) were assessed for allele loss at five dinucleotide repeat microsatellite markers flanking *APC* DNA was extracted from paired samples of peripheral blood and desmoids by standard methods, and polymerase chain reactions PCRs performed using fluorescent-labelled forward primers. Tumour and normal PCR products were analysed on an ABI 377 Prism semiautomated fluorescent DNA analyser, together with GeneScan software (ABI version 2.0.2). Allele loss at informative markers was defined as a reduction in relative peak area of 50 per cent or more Mutation detection was carried out on DNA from these nine and from a further eight desmoids (from another six patients with FAP), together with genomic DNA to allow somatic and germline mutations to be distinguished. PCR products amplified from *APC* exon 15 were subjected to DNA heteroduplx analysis using MDE gel.

Results LOH at *APC* was found in two desmoids. Heteroduplex analysis of DNA showed somatic *APC* mutations in nine desmoids, all lying between codons 1262 and 2005.

Conclusion That LOH or somatic mutation of the wild-type allele occurred in 11 of 17 of the desmoids provides strong evidence that *APC* acts as a tumour-suppressor gene in this tumour type, and argues against a dominant negative mode of action for *APC*. These results also show that the 'second hit' is more often due to a somatic mutation than allelic loss. Somatic mutation or LOH at *APC* may be the only genetic event necessary for desmoid growth.

Is the pneumoperitoneum responsible for the occurrence of port-site metastases?

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Laparoscopic resection for cancer is controversial and port-site metastases are not infrequent. The mechanisms of occurrence of port-site metastases remain unclear. Animal experiments have suggested a role for carbon dioxide (CO_2). On the other hand, port-site metastases also occur after thoracoscopy, where no CO_2 is used, and experienced laparoscopic surgeons have reported hundreds of cancer operations without any port-site recurrence The aim of this study was to define the role of CO_2 in seeding of tumour cells in humans.

Staging laparoscopies for pancreatic cancer were used as a model, because more than 90 per cent of these cancer cells show in a mutation on the k-*ras* gene, allowing the detection of low levels of tumour cells The items CO_2, instruments, trocars, suction device and peritoneal cytology were examined. CO_2 was captured in a Bülau bottle containing pH-controlled culture medium; mean(s.d.) 89(4) per cent of total CO_2 was collected. The presence, viability and the biological significance of cells were investigated using conventional cytology, by a senior pathologist, and trypan blue vital staining. Amount of DNA was assessed with a semiquantitative β-globin polymerase chain reaction (PCR). The k-*ras* gene was amplified and presence of mutations in codons 12 and 13 was determined by restriction fragment length polymorphism analysis. Sensitivity of this PCR was assessed to be less than ten cells. Negative and positive controls were used.

As assessed by conventional cytology, the peritoneal sample was the most cellular (mean(s.d.) $5{\cdot}3 \times 10^5(4{\cdot}1 \times 10^4)$ cells). Instruments ($4{\cdot}9 \times 10^4(4{\cdot}6 \times 10^4)$ cells), trocars ($2{\cdot}9 \times 10^4(2{\cdot}8 \times 10^4)$ cells) and suction device ($7{\cdot}7 \times 10^4(1{\cdot}2 \times 10^5)$ cells) samples were also highly cellular. CO_2 samples contained fewer than ten nucleated cells. DNA (β-globin) contents showed similar distributions. When present, cells were more than 90 per cent viable as assessed by vital staining. Morphologically, the pathologist suspected tumour cells in six of 12 peritoneal samples, four of 11 instruments, four of 12 trocars and two of seven suction devices, but in none of 12 CO_2 samples. After gene amplification, low levels of tumour cells were detected by PCR in four of 12 aerosols. Six aerosols did not contain any DNA, as confirmed by a second PCR. Two aerosols were borderline.

During staging laparoscopy for pancreatic cancer in humans, even in the presence of massive peritoneal contamination, the

Conclusion Inorganic iron in concert with chemical and physical inducers of the HSR are sufficient to trigger apoptosis. The accumulation of iron in injury (haematoma) and in venous stasis ulcers (haemosiderin) may predispose to accelerated apoptosis and account, in part, for failure of wound healing

Prognostic significance and therapeutic consequences of early lymphatic and haematogenous tumour cell dissemination in oesophageal cancer

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Background The concept of endoscopic surgery and local therapy of small primary oesophageal cancers is based upon the assumption that these patients display no metastatic cells. However, current tumour staging procedures fail to detect minimal amounts of disseminated tumour cells present in secondary organs, which might be the seed for subsequent metastatic relapse.

Methods Some 1308 lymph nodes and bone marrow aspirates from 68 patients without overt metastases who had undergone radical *en bloc* esophagectomy (R_0 resection) were evaluated Lymph nodes judged as 'tumour free' by routine histopathology were examined further for the presence of single tumour cells using immunohistochemistry with the antiepithelial monoclonal antibody Ber-EP4, whereas bone marrow aspirates were screened for single tumour cell dissemination with the monoclonal antibody A45-B/B3 The specificity of these methods was demonstrated by consistent negative staining of lymph nodes and bone marrow aspirates from control patients (no carcinoma; $n = 94$).

Results Sixty-seven (17 per cent) of 399 'tumour-free' lymph nodes, obtained from 42 (62 per cent) of 68 patients, displayed Ber-EP4-positive tumour cells Fifteen of the 30 patients staged as free from lymph node metastases (pN_0) had these cells and five of these 15 patients presented with a small primary tumour (pT_{is}–pT_1). Using multivariate Cox analysis, the presence of Ber-EP4-positive cells in 'tumour-free' lymph nodes was an independent factor for a significantly reduced relapse-free survival ($P = 0{\cdot}005$) and overall survival ($P = 0{\cdot}008$). Twenty-five of the 42 patients who had Ber-EP4-positive cells in the lymph nodes also had single tumour cells in the bone marrow aspirates. None of the patients without single lymphatic tumour cell spread showed tumour cell spread in bone marrow aspirates. There was no difference in relapse-free and overall survival between patients with minimal tumour cell spread to lymph nodes and bone marrow. Remarkably, all of the 15 patients who were restaged as lymph node negative by both histopathological and immunohistochemical analyses survived the observation period without recurrence.

Conclusion The frequent occurrence of disseminated tumour cells in patients with apparently localized primary tumours challenges the concept of endoscopic and local surgical treatment A combined histopathological and immunohistochemical examination of excised lymph nodes may imrpove current tumour staging with consequences for adjuvant therapy.

HER2/neu-derived peptide stimulates lymphocytes to recognize and lyse human pancreatic cancer cells *in vitro*

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Background The authors recently showed that the recognition of pancreatic cancer cells by tumour-specific cytotoxic T lymphocytes (CTL) is associated with overexpression of Her2/neu This recognition was human leucocyte antigen (HLA)-A2 restricted. A nine-amino-acid peptide (GP2) derived from the proto-oncogene HER2/neu was identified as an antigen recognized by these CTL

Methods Peripheral blood lymphocytes (PBL) were obtained from patients with pancreatic cancer and healthy volunteers ($n = 3$) (all HLA-A2 positive). After initial activation by anti-CD3 antibody, T cells were expanded in interleukin (IL) 2 50 units ml^{-1} In weekly intervals, PBL were stimulated with allogeneic, GP2-pulsed dendritic cells (DC). DC were generated from healthy HLA-A2-positive donors using IL-3, IL-4 and granulocyte–macrophage colony-stimulating factor Standard ^{51}Cr release assays were performed using DC, DC/GP2, T2, T2/GP2 and five human pancreatic cancer cells (all HER2/neu positive, three HLA-A2 positive, two HLA-A2 positive One of these cell lines was originally HLa-A2 negative, but was transfected with a plasmid encoding HLA-A2. In parallel experiments, effector cells were preincubated with anti-HLA-class I and anti-HLA-A2 monoclonal antibodies (Mab)

Results DC/peptide-stimulated CTL proliferated to therapeutically useful numbers CTL were predominantly DC8 positive (CD8: mean(s d.) 57·9(3·2) per cent; CD4· 6·9(3·5) per cent; CD16. 6(2) per cent; T-cell receptor 77·3(6·9) per cent). CTL recognized GP2-pulsed T2 and DC/GP2 cells significantly better than unpulsed targets (214(39) *versus* 93(2) LU ($P < 0{\cdot}005$) and 2153(333) *versus* 648(126) LU ($P < 0{\cdot}005$)). Furthermore, these CTL showed significantly greater cytotoxicity against HLA-A2 positive pancreatic cancer cells than against HLA-A2-negative targets (427(54) and 251(49) LU *versus* 22(8) and 27(12) LU; $P < 0{\cdot}005$ in each comparison) The HLA-A2 transfected cell line was significantly better recognized than the wild type (HLA-A2 negative) cells (225(71) *versus* 22(8) LU; $P < 0{\cdot}05$). In addition, the cytotoxicity of DC/GP2-stimulated CTL was blocked by Mab to HLA class I and to HLA-A2 ($P < 0{\cdot}001$).

Conclusion *In vitro* stimulation of PBL using allogeneic DC pulsed with GP2 results in CTL which are able to recognize this peptide and to lyse human pancreatic cancer cells. These findings have potential clinical application in adoptive immunotherapy in pancreatic cancer.

Minimal lymphatic tumour cell dissemination in patients with pancreatic cancer: incidence and prognostic significance

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Background Tumour relapse occurs frequently in patients with ductal pancreatic head cancer despite the absence of residual tumour detectable at primary surgery. Therefore it has to be assumed that current tumour staging procedures fail to detect minimal accounts of disseminated tumour cells present in secondary organs, which might be the seed for subsequent metastatic relapse.

Methods Lymph nodes from 18 patients who had undergone radical tumour resection (R_0 resection) were evaluated. Lymph nodes judged as 'tumour free' by routine histopathology were further examined for the presence of single tumour cells using immunohistochemistry with the antiepithelial monoclonal antibody Ber-EP4.

Results Sixteen of 37 'tumour-free' lymph nodes, obtained from 13 of 18 patients, displayed Ber-EP4-positive tumour cells. Twelve of these 18 patients presented with a pT_2 stage. Nine of 12 patients staged as pN_0 had cells. Two of six pN_1 patients had no Ber-EP4-positive cells in histopathologically tumour-free lymph nodes. Using multivariate Cox regression analysis, the presence of Ber-EP4-positive cells in 'tumour-free' lymph nodes was an independent factor for a significantly reduced relapse-free survival ($P = 0{\cdot}006$) and overall survival ($P = 0{\cdot}01$). Remarkably, none of the patients who were restaged as lymph node negative by both histopathology and immunohistochemistry developed tumour relapse during the observation period.

Conclusion The frequent occurrence of disseminated tumour cells in patients with pancreatic cancer and their prognostic impact supports the need for a refined staging system of excised

(LacZ) and FITC-labelled oligodeoxynucleotide (FITC-ODN) were prepared. HVJ–liposome or HVJ–cationic liposome was prepared as follows. Dried lipids containing phosphatidylserine or DC cholesterol were mixed for liposome or cationic–liposome respectively. These suspensions were incubated with DNA or FITC-ODN and inactivated HVJ. Hep3B and Huh7(human hepatoma cell line) were transfected with these liposome complexes. These were injected directly into Wistar rat liver *in vivo*. To detect the cellular uptake of FITC-ODN, transfected cells or livers were examined by fluorescence microscopy X-gal staining was performed 72 h after the injection of HVJ–liposome containing LacZ. The complementary DNA of the human CK-BB gene was kindly provided by Dr Wieringa. HVJ–liposome containing the CK gene with CAG promoter was transfected *in vitro* and *in vivo*. Transgene expression of CK was analysed by reverse transcriptase–polymerase chain reaction (RT-PCR).

Results After transfection of HVJ–liposome containing LacZ, only 2 or 3 per cent of the Hep3B and Huh7 cells were positive on X-gal staining. However, fluorescence was detected in almost all cells even at 30 min after transfection of HVJ–cationic liposome containing FITC-ODN, especially 50–60 per cent of nucleus of cells were accumulated. X-gal staining of rat liver transfected with HVJ–liposome containing LacZ revealed that 57 per cent of hepatocytes were positive. In contrast, fluorescence was observed only in non-parenchymal cells *in vivo* after transfection of HVJ–cationic liposome containing FITC-ODN, probably because of intereference by non-parenchymal cells. Transcripts of the CK gene were positive in Hep3B 24 h after transfection of HVJ–cationic liposome containing the CK gene with RT-PCR Also clearly detected were transcripts of the CK gene in rat liver tissues 24 h after the injection of HVJ–liposome containing the CK gene

Conclusion *In vitro* the efficiency of gene transfer and expression with the HVJ–cationic liposome was much higher than with the HVJ–liposome method. However, HVJ–cationic liposome introduced the marker genes *in vivo* to non-parenchymal cells, and not to hepatocytes. The HVJ–liposome method was successfully employed for *in vivo* gene transfer to the liver. The HVJ–liposome-mediated gene transfer system is an attractive method for targeting gene transfer of parenchymal or non-parenchymal cells. Further study will be necessary to evaluate the expression or function of the CK transferred to the liver.

Obstetric anal sphincter damage assessed prospectively in the early postnatal period

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Currently, anal sphincter trauma is thought to occur in up to 35 per cent of primiparous women at the time of vaginal delivery. In multiparous women as a whole, this increases by 5 per cent with further vaginal delivery, but the incidence is not quantified in relation to each subsequent normal delivery. In addition, referral rates to repair damaged sphincters imply fewer injuries than those quoted. Using a continence questionnaire, endoanal ultrasonography (10 mHz) and simple anorectal manometry, 150 consecutive women were assessed within 72 h after delivery (93 para-1, 57 para-2) over a 6-week period. median age was 24 (range 15–43) years. Modes of delivery included normal vaginal delivery (NVD), forceps (F), elective (EL) and emergency (EM) caesarian sections. One third-degree tear occurred in a para-2 NVD case and matched an endosonographic defect.

The incidence of latent anal sphincter injuries was 10 per cent for both para-1 and para-2 vaginal deliveries. Amongst the para-1 group, NVD had an incidence of 6 per cent, whilst for F this was 60 per cent. For the para-2 group, these incidences were 7 and 50 per cent respectively. The incidence of anal sphincter trauma increases by 1 per cent with a second NVD. There were no sphincter defects detected amongst the EL and EM groups in either set.

It is concluded that these injuries can be identified using a simple well tolerated technique before discharge from the maternity unit, allowing intervention to prevent further damage during subsequent vaginal deliveries.

Endothelial cell apoptosis is accelerated by inorganic iron and heat via an oxygen-radical dependent mechanism

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Background Iron participates in diverse pathological processes via the Fenton reaction which catalyses the formation of reactive oxygen species (ROS). To test the hypothesis that this reaction accelerates apoptosis, human umbilical vein endothelial cells (HUVEC) were used as surrogates for the microvasculature *in vivo*.

Methods HUVEC were loaded with Fe^{3+} 20 $\mu mol\ l^{-1}$ using 8-hydroxyquinolin as carrier and then challenged with sodium arsenite (As) 40 $\mu mol\ l^{-1}$ or heat (43°C) which stimulate the heat shock response (HSR). The iron dependence was tested using the selective chelator *o*-phenanthroline (Ph) and the role of ROS was assessed using superoxide dismutase (SOD), catalase (CAT) and the ROS reporter dye dichlorofluorescein diacetate (DCFDA).

Results Iron-loaded HUVEC executed apoptosis following a heat shock stimulus as demonstrated by electron microscopy, TUNEL stain and plasma membrane phosphatidyl serine mobilization (Annexin V stain). Apoptosis induced by As 40 $\mu mol\ l^{-1}$ (+) was blocked by Ph (◆), SOD (■) and CAT (▲) (*Fig. 1*). Iron-loaded HUVEC also loaded with DCFDA showed ROS after HSR but before apoptosis (*Fig 2*).

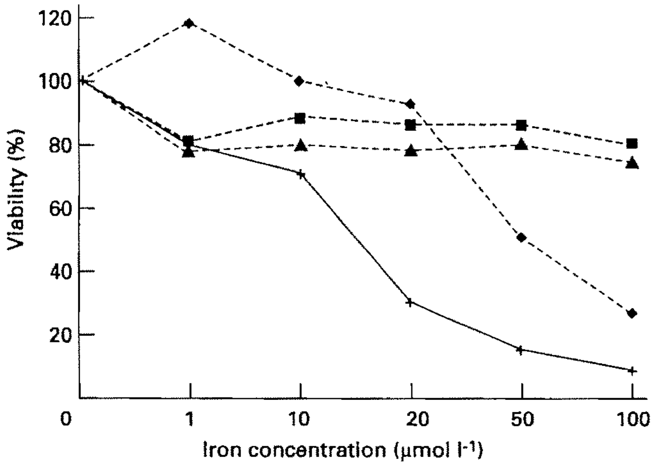

Fig. 1

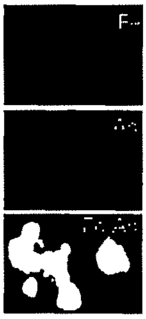

Fig. 2

histocompatibility complex-mismatched Lewis (RT1^{l}) to Buffalo (RT1^{b}) rat cardiac or renal allograft was compared with that of OX-38 Rejection determined by cessation of cardiac pulsation or fatal uraemia was confirmed histologically.

Results RIB 5/2 administration induced tolerance to heart allografts combined with either IV or IT route of alloantigen administration while only when given with IV alloantigen did tolerance develop to renal allografts. In contrast, depleting OX-38 with IV SC administration failed to prolong both heart and renal allografts, while OX-38 with IT SC induced tolerance only to heart grafts

	Treatment 21 days before transplant		MST	
Group	Splenocytes	Anti-CD4 Mab	Heart graft	Kidney graft
1	—	—	7(1)	10(0)
2	LEW IT	—	7(1)	—
3	—	OX-38	8(1)	—
4	LEW IT	OX-38	> 140(57)*	15(2)
5	LEW IV	OX-38	8(3)	19(13)
6	—	RIB 5/2	7(1)	10(1)
7	LEW IT	RIB 5/2	> 119(69)*	18(17)
8	LEW IV	—	11(2)	—
9	LEW IV	RIB 5/2	> 120(70)*	> 93(58)*

Values are mean(s.d.). *$P<0.01$ *versus* group 1 (Mann–Whitney *U* test)

Conclusion While the route that concomitant alloantigen is given by is important (IV *versus* IT), the modulation of CD4-positive recipient cells by non-depleting RIB 5/2 is more potent in the induction of allograft tolerance than is elimination of these CD4 positive cells with depleting OX-38.

Randomized dose study of tissue plasminogen activator for pulse-spray thrombolysis

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Background The authors have previously reported rapid thrombolysis (median duration 120 min) with mean(s.d) 83·6(7·7) per cent cumulative limb salvage rate at 18 months' follow-up with pulse-spray thrombolysis (PST) using 0·33 mg ml^{-1} tissue plasminogen activator (rt-PA) in the management of limb ischaemia. It was hypothesized that rapid thrombolysis can be achieved with PST using a very low dose of rt-PA.

Methods With hospital ethics committee approval and informed consent, 36 patients with limb ischaemia eligible for PST were randomized to receive thrombolysis with 0·16, 0·33 or 0·5 mg ml^{-1} rt-PA as a 0·2-ml bolus every 30 s

Results

	0·16 mg ml^{-1}	0·33 mg ml^{-1}	0·5 mg ml^{-1}
Age (years)	68 (65–73)	76 (71–80)	73 (62–78)
Duration of symptoms (days)	17 (7–35)	18 (8–28)	8 (6–14)
Length of occlusion (cm)	14 (10–20)	35 (10–60)	20 (10–30)
Prelysis ABI	0·1 (0–0·5)	0 (0–0·3)	0·1 (0–0·3)
Total dose (mg)	7·4	18·7	25·2
Duration of lysis (min)	95 (80–180)	120 (75–160)	120 (90–205)
Post-lysis ABI	0·8 (0·3–1)	0·8 (0–0·9)	0·9 (0·2–1)

Values are median (interquartile range). No significant difference was found between the three groups (Kruskal–Wallis analysis of variance)

Conclusion Rapid thrombolysis with PST can be achieved using a very low dose regimen using rt-PA in a concentration of 0·16 mg ml^{-1}.

Colorectal cancer mutations in whole gut lavage fluid

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Detection of tumour-specific mutations holds promise as a tool for early diagnosis and screening for colorectal cancer (CRC). Such mutations can be detected in stool and colonic washings and so could be exploited for population cancer screening when combined with robotic analysis The value of colonic washings has been assessed (in the form of whole gut lavage fluid (WGLF)) for analysis of mutations in four genes commonly altered in CRC. DNA was extracted from 100 ml of WGLF obtained before operation from 40 patients undergoing cancer resection Tumour DNA was extracted from the corresponding paraffin sections and analysed for Ki-Ras (codon 12) mutations by direct sequencing and p53 (codon 248) mutations by restriction enzyme digestion. Single-strand conformational polymorphism (SSCP) analysis was used for both the mutation cluster region of the adenomatous polyposis coli (APC) gene and the transforming growth factor beta receptor II (TGFβ RII) gene. In all, 26 mutations were detected in 18 of 40 primary tumours (seven Ki-Ras, two p53, two TGFβ RII and 15 APC mutations).

To assess the ability of the techniques to detect any human DNA in the WGLF, mitochondrial fragments cytochrome b and oxidase were analysed by polymerase chain reaction and were amplifiable in 37 of 40 samples. Analysis of cancer-specific mutations in WGLF consisted of a PCR/restriction enzyme enrichment strategy for Ki-Ras and p53 mutations, while APC and TGFβ RII mutations were analysed by non-enriched SSCP Two of seven Ki-ras, both p53 mutations, none of 15 APC mutations and neither of two TGFβ RII mutations were detected in the WGLFs.

In this series 18 patients had the potential for a genetic diagnosis of their cancer and four mutations were detected in the WGLF These preliminary findings indicate that stool-based genetic diagnosis will require selective mutation enrichment and that other methods commonly used for mutation detection, e.g SSCP, are too insensitive Additional methods of mutation enrichment must be sought if these tests are to be used for screening.

Liver-directed gene transfer by haemagglutinating virus of Japan–liposome method

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Background In liver surgery, several stress factors such as prolonged hepatic ischaemia or an excessive hepatectomy often lead to fatal liver damage Effective liver-directed gene therapy may provide a means to introduce exogenous functional genes into hepatic cells to alter this pathological process. In order to induce tolerance of the liver to surgical stress, the authors introduced a highly efficient haemagglutinating virus of Japan (HVJ)–liposome-mediated transfer method. The induced acceleration of regeneration after major hepatectomy or endotoxin tolerance in transgenic mice livers expressing creatine kinase (CK) has been reported previously. The CK gene has been transfected to the liver *in vitro* and *in vivo* using the HVJ–liposome method.

Methods To investigate the efficiency of the gene transfer system, β-galactosidase gene with chicken β-actin promoter relationship between changes in intracellular calcium ([Ca^{2+}]i) and secretion in individual human parathyroid cells. The cells were dispersed from tumours removed from patients with primary HPT ($n=9$) and maintained in primary culture in RPMI 1640 medium on Pronectin-coated coverslips.

[Ca^{2+}]i was measured as the ratio of the fluorescence of Fura2-loaded cells excited at 340 and 380 nm ($R_{340/380}$), and secretion was measured simultaneously using the non-permanent fluorescent membrane indicator dye FM1-43 by means of an inverted fluorescent microscope with an intensified camera and IonVision image analysis software. A reduction of extracellular calcium ([Ca^{2+}]ext) from 3 mmol l^{-1} to 0·5 mmol^{-1} decreased [Ca^{2+}]i (mean(s.d.) $R_{340/380}$ from 1·3(0·5) to 0·7(0·3); $n=25$ cells) and increased FM1-43 fluorescence (from mean(s.d.) 67·2(21·8) to 94·3(15·8) units). At 3 mmol l^{-1} [Ca^{2+}]ext, reducing [Ca^{2+}]i by an intracellular calcium chelator 1,2bis(*o*-aminophenoxy)ethane-N,N,N′,N′-tetracetic-acid-tetra(acetoxymethyl)ester BAPTA/AM 10 μmol l^{-1} or by depolarization with high potassium (50 mmol l^{-1}) increased FM1-43 fluorescence by 35 per cent of the initial signal. Addition of adenosine 5′-triphosphate 50–100 μmol l^{-1} when the [Ca^{2+}]ext was reduced to 0·5 mmol l^{-1} increased [Ca^{2+}]i to values similar to those induced by 3 mmol l^{-1} [Ca^{2+}]ext and prevented the rise in FM1-43 signal.

Using a laser-scanning confocal microscope (Leica TCS), individual cells incubated in FM1-43 at 3 mmol l^{-1} [Ca^{2+}]ext showed fluorescence in a compartment associated with the plasma membrane. On reduction of [Ca^{2+}]ext to 0·5 mmol l^{-1} in the continued presence of dye, this fluorescence rapidly increased (1–2 min) and was later seen inside the cells (5–8 min). The initial increase is consistent with a rise in the cell surface area due to fusion of secretory granules with the plasma membrane during exocytosis. The later internalization of FM1-43 is consistent with recycling of the granule membrane by endocytosis after the secretory burst. Cells incubated at low [Ca^{2+}]ext with FM1-43 for 45 min accumulated the fluorescent dye in the cytoplasm, with a granular pattern suggesting targeting to secretory granules. When the external dye was then removed, the intensity of the staining was stable at high [Ca^{2+}]ext, but rapidly decreased if the [Ca^{2+}]ext was stepped down to 0·5 mmol l^{-1} (from 49·3(11·7) to 32·6(14·2 units); $n=15$ cells) or if the cells were treated with BAPTA/AM at 3 mmol l^{-1} [Ca^{2+}]ext (from 58·2(17·4) to 36·5(14·9) units; $n=11$ cells). The rapid removal of dye on reduction of [Ca^{2+}]i confirms that FM1-43 is internalized into a secretory compartment.

These results, using FM1-43 fluorescence to indicate membrane turnover during secretion from individual human parathyroid cells, show that the main modulator of secretion is low [Ca^{2+}]i, not [Ca^{2+}]ext. Further studies will investigate the hypothesis that decreased expression or function of the plasma membrane calcium receptor in hyperparathyroidism permits the cells to maintain a low [Ca^{2+}]i and high secretory rate in the face of high [Ca^{2+}]ext.

Random flap survival improvement with the use of nitric oxide precursors

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Background Nitric oxide (NO) is produced by NO synthase using L-arginine as a substrate. This enzyme can be blocked competitively by substances such as (*N*ψ-nitro-L-arginine methylester (L-NAME). Investigators have shown that L-arginine may aid in reducing reperfusion injury, scavenging free radicals, as well as acting as a vasodilator. The distal most aspect of random flaps can be considered an areas of ischaemia and gradual reperfusion and methods of decreasing reperfusion injury may therefore be applicable. The dorsal rat flap has been a reliable model of a flap with an axial pattern of vascularity and a random extension which will give a predictable percentage of necrosis. This study determined the potential effect of L-arginine on survival of random skin flaps in a rat model, assessed whether the potential improved survival is mediated through decreased leucocyte sequestration as with island flap ischaemia-reperfusion models, and examined how the effects of L-arginine would be modified after blocking NO production.

Methods The model used was a modification of the McFarlane rat dorsal skin flap based on a caudal vascular blood supply. Fifty-five female Sprague–Dawley rats, each weighing 250–300 g, underwent general anaesthesia with an intraperitoneal injection of sodium pentobarbital 45 mg kg^{-1}. Dorsal skin flaps measuring 3 × 10 cm were raised, and resutured back to their original positions. Control groups included creation and elevation of the flap. Some 30 min before elevation of the flaps the animals received a 1-ml intraperitoneal injection of either saline or test substance: group 1 (control), normal saline, flap elevation ($n=17$); group 2, L-arginine 300 mg kg^{-1} in normal saline, flape levation ($n=18$); group 3, flap elevation, L-NAME 465 mg kg^{-1} + L-arginine 300 mg kg^{-1} in normal saline ($n=6$); and group 4, L-arginine 300 mg kg^{-1} in normal saline, flap elevation and then intraperitoneal L-arginine 300 mg kg^{-1} twice daily for 5 days ($n=12$). Some 24 h after operation, a full-thickness skin biopsy measuring 0·2 × 0·5 cm was taken from the distal third of the flap, to assess the number of neutrophils (NPLs) present in the flap. The skin biopsies were placed in a 10 per cent formalin solution and sections stained with haematoxylin and; sections were also fresh-frozen and subjected to myeloperoxidase assay to assess the number of neutrophils present and neutrophil counts were taken per 20 high-power fields (NPLs/20HPF) in order to determine neutrophil sequestration in the flap. The rats were then allowed to survive for a period of 1 week, at which point viability of the flaps was determined and the surviving and dead parts of the flap traced to assess their surface. At the end of the week the animals were killed using carbon dioxide chamber according to institutional policy. Statistical evaluation between group means was performed with analysis of variance using the Neumann–Keuls post hoc test for multiple comparisons.

Results The use of L-arginine decreased the amount of necrotic flap from mean(s.d.) 43·1(1·6) per cent (control flaps) to 33·7(2·0) per cent ($P<0·01$) with one dose and to 26·4(3·8) per cent with a 5-day dosage. The use of L-NAME increased the amount of necrosis to 59·5(3·0) per cent ($P<0·01$). The NPLs/20HPF counts of the flaps followed the same pattern with 82·7(10·4) NPLs/20HPF in control flaps, 47·0(8·1) NPLs/20HPF in L-arginine-treated flaps ($P<0·01$ *versus* control), 88·7(15·1) NPLs/20HPF in L-arginine plus L-NAME-treated flaps and 43·1(4·0) NPLs/20HPF with a 5-day dosage.

Conclusion Administration of L-arginine before random flap elevation can significantly reduce the extent of flap necrosis due to reperfusion injury. This protective effect is completely neglected by the use of L-NAME, while there may be a trend for improved survival after longer periods of administration. The number of NPLs in the flap correlates with the extent of flap necrosis. Since L-arginine reduces the number of NPLs and the extent of flap necrosis only in the presence of active NO synthase, it is hypothesized that the protective effect of L-arginine is due to a NO-mediated suppression of NPL-mediated injury.

Tolerance to heart and kidney grafts induced by non-depleting anti-CD4 monoclonal antibody (RIB 5/2) *versus* depleting anti-CD4 monoclonal antibody (OX-38) with donor antigen administration

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Background Reliable tolerance to organ allografts has remained elusive. Intrathymic (IT) administration of donor splenocytes (SC) with either non-depleting anti-CD4 monoclonal antibody (Mab) (RIB 5/2) or depleting anti-CD4 Mab (OX-38) induced tolerance to heart, but not renal, grafts, while intravenous (IV) administration of SC plus OX-38 failed to prolong both heart and renal allografts.

Methods In this study, the efficacy of a single intraperitoneal dose of 20 mg kg^{-1} RIB 5/2 plus IV or IT donor antigen (25×10^6 SC) pretreatment on day 21 before either a major

		No. of patients with sensory deficit		No of patients with reduced movement at 3 months	
	n	At discharge	at 3 months	Abduction	Flexion
ICBN preserved	40	18 (45)	22 (61)	25	19
ICBN divided	80	67 (84)*	56 (80)	49	39

Values in parentheses are percentages. $P<0·001$ *versus* ICBN preserved

ICBN preservation is possible in the majority of patients but does not provide long-term (3 months) benefit in terms of reduction of sensory and motor function.

Contrast enhancement magnetic resonance imaging and tumour angiogenesis in breast cancer

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Background Patterns of contrast enhancement in magnetic resonance imaging (MRI) of breast cancers may in part be accounted for by differences in tumour vascularity. The aim of this study was to compare preoperative subtraction contrast enhancement patterns on MRI with detailed histopathological angiogenic mapping of resected tumour specimens.
Method Twenty-one patients with breast cancer were studied. Breast MRI was performed with and without contrast enhancement before operation, using a transverse T1-weighted three-dimensional (3D) FLASH sequence. Pre- and post-contrast 3D data sets were matched by a rotational and translational registration algorithm to correct for interscan motion Subtraction of the registered data sets generated subtraction images. Following resection, the fixed specimens were sliced in a transverse plane and whole block sections were prepared. Immunohistochemical staining was performed with monoclonal antibodies for markers of food vessel endothelium (factor VIII, CD34, CD31). The distribution and density of microvessels in the whole section was mapped in detail and compared with subtraction images from contrast-enhanced breast MRI.
Results In serial tumour sections, similar microvessel distributions were seen with the three endothelial markers. Patterns of magnetic resonance enhancement included rim ($n=3$), homogeneous ($n=5$), heterogeneous ($n=9$) and diffuse patchy ($n=4$) enhancement. Microvessel density correlated with the extent of contrast enhancement.
Conclusion Subtraction contrast-enhanced MRI provides a quick and reliable method for assessing enhancement patterns. This technique may prove useful in estimating the angiogenic activity of breast carcinomas before operation

Role of desmosomal cadherins in the adhesion and invasion of human breast cancer cells

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Background Breast cancer is the commonest female cancer in the UK. It is invasion and distant metastasis which determines long-term prognosis in these patients This study assessed the role of desmoglein 2 (Dsg2), a novel desmosomal cadherin, and E-cadherin (E-cad) in the adhesion and invasion of human breast cancer cells.
Methods Three human breast cancer cell lines were used, MDA MB 231, MCF7 and BT474. Expression of Dsg2 and E-cad was determined with Western blotting and immunocytochemistry. Cell aggregation, *in vitro* invasion and colloidal gold phagokinetic assays were used to study cell-cell aggregation, invasion and migration in these cells These functions were compared in cancer cells alone and cells treated with a monoclonal antibody (Mab) to Dsg2 with or without E-cad Mab.
Results All cell lines expressed Dsg2 MCF7 and BT474 were E-cad positive, but MDA MB 231 cells were E-cad negative. Treatment with Dsg2 Mab significantly reduced cell–cell aggregation in all three cell lines. median aggregation indices at 30 min (median(s.d.), control *versus* Mab) were 0·7(0·3) *versus* 0(0·5) (*$P<0·05$, Wilcoxon signed rank test), 0·7(0·1) *versus* 0·4(1·5) ($P<0·05$) and 0·7(0·2) *versus* 0·2(0·3) ($P<0·05$) respectively. Mab to E-cad reduced cell–cell aggregation in MCF7 and BT474 cells but had no significant effect in MDA MB 231 cells. Both the *in vitro* invasive potential and cell migration in colloidal gold were increased in pretreated cells
Conclusion It is proposed that Dsg2 is an important adhesion molecule in addition to E-cad, which regulates the invasion and metastasis of human breast cancer cells.

Effect of antioestrogens on the 'high-risk' breast

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Women at increased risk of breast cancer by virtue of a strong family history are being randomized to preventative tamoxifen despite a lack of knowledge and of its effect on normal breast tissue. Here the effects of tamoxifen and a novel pure antioestrogen (ICI 182780) on normal breast tissue from women at high risk of breast cancer ($n=3$) and normal tissue removed away from benign lesions ($n=3$) and implanted into athymic nude mice is reported. Tissue from each subject was inserted subcutaneously into the flank ($n=16$ mice) and 2 weeks later mice were treated either with a slow-release oestradiol pellet (2 mg E_2; $n=12$) or control pellets ($n=4$) A week later mice were treated with tamoxifen (1 mg day^{-1}; $n=4$), ICI 182780 (5 mg week^{-1}; $n=4$) or vehicle control ($n=8$) injections for 2 weeks. Implants were removed for histological examination and assessment of progesterone receptor (PR) expression and proliferation (Ki67 antigen) using immunocytochemistry at weeks 2, 3, 4 and 5.

Of 366 implants retrieved, 252 contained normal breast lobules (68·9 per cent). In both groups there was a significant rise in Ki67 and PR expression after E_2. In the 'high-risk' group, tamoxifen had no significant effect on PR or Ki67 expression. After ICI 182780, PR expression fell significantly from mean(s.d.) 31(7) per cent cells positive in the E_2 alone group to 16(11) per cent ($P=0·015$, Mann–Whitney *U* test) and Ki67 fell significantly from 8(6) to 3(3) per cent ($P=0·03$). In the 'normal-risk' group, neither drug had a significant effect on PR expression, but tamoxifen and ICI 182780 reduced Ki67 expression to near control levels (3(2) and 3(2) respectively) In conclusion, the 'high-risk' breast, even one known to harbour a mutation in BRCA 1 responds to oestrogen stimulation. This response is unaffected by tamoxifen, but is significantly inhibited by ICI 182780, suggesting that this drug may be a better preventative agent

Imaging exocytosis in human parathyroid cells by confocal and fluorescent microscopy with the fluorescent dye FM1-43

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To investigate the abnormal calcium-controlled secretion of parathyroid hormone in primary hyperparathyroidism (HPT), time lapse fluorescent cell imaging was used to determine the

Cyclin D1 overexpression in oestrogen receptor-positive breast cancer predicts poor prognosis

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Cyclin D1 (CD1) is a key cell-cycle regulatory protein implicated to have significant oncogenic activity in a variety of malignancies CD1 is overexpressed in up to 50 per cent of breast carcinomas yet little is currently understood of the functional consequences in this disease

The authors have previously confirmed a strongly positive correlation betwen CD1 messenger RNA (mRNA) and oestrogen receptor mRNA ($P = <0{\cdot}0001$) in a large series of operable breast carcinomas. Clinicopathological features of these patients have now been investigated in relation to CD1 (258 patients with Stage 1–2 lesions; median follow-up 75 months).

Overall, there were no significant correlations between clinicopathological features and CD1 mRNA. However, when analysed as oestrogen receptor-positive ($n = 185$) and oestrogen receptor-negative ($n = 73$) subgroups, high levels of CD1 were significantly associated with reduced disease-free interval ($P = 0{\cdot}001$), shorter time to local recurrence ($P = 0{\cdot}021$), metastasis ($P = 0{\cdot}015$) and reduced overall survival ($P = 0{\cdot}022$) in oestrogen receptor-positive patients. There was no correlation with disease-free interval for adjuvant hormone or chemotherapy.

Overexpression of CD1 mRNA appears to predict reduced disease-free interval and survival in oestrogen receptor-positive breast cancer. These findings support conclusions from other studies suggesting that within the oestrogen receptor-positive phenotype overexpression of CD1 predicts a worse outcome which may benefit from more aggressive treatment.

Improving residents' breast cancer clinical skills with the structured clinical instruction module: results of a multi-institutional study

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Background The purpose of this study was to determine, in a multi-institutional setting, the effectiveness, portability, and feasibility of the Structured Clinical Instruction Module (SCIM) as an instructional format for surgical residents.

Methods The breast cancer SCIM is an abbreviated (3 h) clinical skills course that places residents in realistic clinical settings. The curriculum encompasses all aspects of assessment of patients with breast cancer. The SCIM was administered to residents ($n = 107$) at four institutions. Fifty-four faculty members and 42 patients participated. All participants were surveyed with multi-item questionnaires. The residents were also asked to perform a self-assessment of their skills before and after the SCIM.

Results The SCIM was delivered at all institutions without difficulty. All participants rated the SCIM highly (from 'above average' to 'outstanding'). Mean ratings (on a five-point scale) for the overall effectiveness of the SCIM as an educational format were as follows:

	Institution			
	A	B	C	D
Patients	4·75	4·73	4·56	4·56
Faculty members	4·47	4·57	4·82	4·76
Residents	4·38	4·75	4·29	4·36

The pretest mean (on a five-point scale) on the self-assessment was 2·53 ('less than adequate'); the post-test mean was 3·66 ('adequate plus') ($P < 0{\cdot}0001$)

Conclusion Residents are acutely aware of their deficiencies in the understanding of breast cancer. The SCIM is a standardized, reproducible, portable and effective educational vehicle.

Primary culture of epithelial cells derived from human breast tumours

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Most *in vitro* studies on breast cancer utilize established cell lines, many of which were first described over 20 years ago Although much useful information has been derived from these, it is likely that genetic aberrations will have occurred over time, so they may not be truly representative of the tumour from which they were derived. Studies using breast primary material are limited, mainly because epithelial cells can be difficult to grow and are often poorly characterized. An improved method has been developed for isolation and culture of epithelial cells derived from breast tumours.

Tumours ($n = 88$; mean patient age 63 (range 38–90) years) were dispersed enzymatically and epithelial cells separated from stromal cells by differential centrifugation. Cells were plated in selective medium and phenotypic integrity confirmed by immunostaining and flow cytometry.

The tumour types which yielded successful cultures are illustrated below.

Histology	Epithelial growth	No epithelial growth
Ductal ($n = 72$)	42 (58)	30 (42)
Lobular ($n = 11$)	6 (54)	5 (45)
Miscellaneous ($n = 5$)	2 (40)	3 (60)

Values in parentheses are percentages

Additionally, epithelial cultures were more likely to be established from tumours of grades II/III and from patients in the fourth to sixth decades, tumour stage or lymph node metastasis was unimportant. These cells have been maintained in culture for up to 3 months without any appreciable phenotypic change

This study demonstrates that epithelial cells can be isolated successfully from breast tumours and maintained as an individual population. These cultures offer a simple and reproducible alternative for *in vitro* studies, which are likely to yield results with greater clinical relevance than work using cell lines.

Randomized prospective study of preservation of the intercostobrachial nerve in axillary node clearance

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Division of the intercostobrachial nerve (ICBN) during axillary node clearance (ANC) may lead to numbness and paraesthesia in the area of its distribution. To determine whether there is any benefit from preserving the nerve 120 patients were randomized to have either preservation or division of the ICBN at surgery. Sensation, shoulder movements and arm circumference were assessed objectively before operation, on discharge and at 3 months. Time taken to complete the ANC was recorded and the adequacy of the clearance determined by the number of nodes cleared Patients completed a questionnaire at 3 months.

Of the 60 patients randomized to preservation of ICB, 21 had the nerve divided in order not to compromise clearance or because of technical difficulty. One patient had the nerve preserved by mistake. Fourteen did not attend at 3 months follow-up. Preserving the nerve increased operative time by median 5 (range 5–15) min. Total node yield did not differ between groups. The range of shoulder movement was similar in each group.

Methods Some 208 dyspeptic patients attending for routine diagnostic endoscopy were recruited into this study. Before endoscopy, specimens were collected of saliva, supragingival and subgingival dental plaque, tongue scrapings and oropharyngeal swabs At endoscopy, gastric antral biopsy was performed for the rapid urease test, culture and (in some patients) histology. Gastric juice samples were aspirated and, in 50 patients, duodenal aspirate also. The polymerase chain reaction (PCR), with primers targeted to the 16S ribosomal RNA sequence of *H pylori*, was also employed for each of the specimens. In patients in whom *H pylori* was detected from multiple sites, restriction endonuclease digestion with HaeIII was performed to determine if the sites were epidemiologically linked

Results and conclusion Some 15 208 patients (7 per cent) had *H pylori*-positive dental plaque but no other oral sites were positive. Using PCR, all 15 had positive antral biopsy and gastric juice specimens and there were five positive duodenal aspirates Four of the dental strains had restriction patterns similar to those of the stomach and duodenal sites, providing evidence that these sites were infected with the same strain.

Analysis of chromosomal aberrations and isolation of novel amplified genes in primary gastric cancers by comparative genomic hybridization

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Comparative genomic hybridization (CGH) analysis was applied in 58 primary gastric cancers to screen for DNA sequence copy number changes and gene amplifications that commonly occur in gastric cancer. Losses were often involved in 1p34–35, 3p21–24(*FHIT*), 5q13–23(*APC*), 6q13–16, 9p23–24(*p16*), 16q, 17p13(*p53*), 18q11–21(*DCC*), 19, 21q and 22q Gains were often involved in 1p36, 8q21–24(c-*MYC*), 16p 20(*PCNA*), Xp21–22 and Xq23–27

These chromosomal regions will contain genes which contribute to gastric cancer development and progression The amplifications of c-*met*, c-*myc*, kis-*ras*, *int-2*, *cyclin E*, and c-*erB2* were detected by CGH Novel gene amplifications were identified in 8p23·1 in about 10 per cent of advanced gastric cancers By screening cosmid clones and EST markers in this region, one fragment of the novel amplified gene was isolated Genomic southern blot revealed its amplification in about 20 per cent of advanced gastric cancers This gene was often overexpressed in advanced gastric cancers and lymph node metastases, suggesting that this amplification may relate to the progression of gastric cancer

CGH is powerful tool for direct screening of chromosomal aberrations and gene amplifications among all chromosomes.

Interventional magnetic resonance guided excision of benign breast tumours

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Background Interventional magnetic resonance (MR) machines have produced unique opportunities for image-guided surgery The open configuration design and fast pulse sequences allow virtually 'real-time' intraoperative scanning to monitor the progress of a procedure, with new images produced every 1 5 s. This study was undertaken to assess the potential use of the machine for image-guided breast surgery

Methods Six women (age range 20–47(median 27·5) years) with palpable benign tumours (by ultrasonography and/or fine-needle aspiration criteria) underwent excision biopsy under general anaesthesia in a General Electric Signa SP10 0·5T interventional MR machine. Lesions were localized before and after contrast (intravenous gadolinium DTPA 20 mmol kg^{-1}) with sagittal and axial fast multiplanar spoiled gradient recalled conventional Signa sequences (flip angle 60°, slices 6×0 mm). Preoperative 'real-time' fast gradient recalled sequences (flip angle 60°, slices 3×0 mm) were also obtained using the flashpoint tracking device. The maximum dimensions of each lesion were measured from the resulting images. The lesions were excised using titanium instruments and an ultrasonically activated scalpel. Intraoperative real-time scanning was performed to demonstrate the resection margin. Signa and real-time images were obtained at the end of the procedure to confirm complete excision. The maximum dimensions of the specimens were compared with those from the images.

Results All tumours were visualized with both Signa and real-time imaging and all enhanced with contrast. Two were visualized only after contrast enhancement. Intraoperative real-time imaging clearly demonstrated a resection margin in all cases. Maximum dimensions on histological examination (range 8–50 (median 26 5) mm) were not significantly different from those measured from Signa ($P>0{\cdot}21$, Student's paired t test) or real-time images ($P>0\ 26$). There was no significant difference between lesion size from Signa and real-time images ($P>0{\cdot}22$). All postprocedure scans clearly demonstrated complete excision. There were four fibroadenomas, one discrete focus of sclerosing adenosis and one schwannoma.

Conclusion Intraoperative MR scanning reliably identifies palpable breast tumours and is sufficiently accurate to guide surgical excision. Further work can now be performed using MR guidance for the excision of impalpable lesions

Sentinel axillary lymph node: helpful in axillary management in patients with breast cancer?

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Background It has been suggested that intraoperative dye injection of breast cancer may opacify the first ('sentinel') axillary lymph node (SN), and that its status could accurately reflect that of the axilla. This information would allow selective axillary dissection or sparing, thus reducing unnecessary surgery, morbidity and cost.

Methods Seventy-nine women with 80 breast cancers who were undergoing mastectomy and axillary clearance (69) or wide local excision and axillary clearance (11) for operable (T_{1-4}, N_{0-2}, M_0) breast cancer were investigated Some 5 ml methylene blue dye was injected into and around the tumour after induction of anaesthesia. During axillary dissection the SN, if found, was removed separately, and then the axilla was cleared. The frequency of SN involvement was correlated with total axillary gland involvement.

Results The SN was identified at operation in 32 cases (40 per cent) In many cases this necessitated extensive dissection. Locations were: level I, 23; level II, 5, level III, 0; not specified, 4 In a further eight cases the node was found during bench dissection In 40 instances (50 per cent) dye was not demonstrated in any gland. There was malignant axillary node involvement in 41 specimens; the SN was involved in 12 (29 per cent true positive), and not involved in five (12 per cent false negative). Thus, if the SN was detected it accurately predicted axillary status, either positive or negative, in 35 instances

Conclusion The SN was opacified by dye injection in less than half of the cases; in some of these extensive dissection was required to locate it Involvement of the SN reflected the total axillary status with impaired accuracy encephalopathy using number connection testing was strongly predictive of survival (A and B *versus* C; $P<0·0001$) as well as being superior in identifying patients with Child disease who have a higher risk of death. The predictive power of Child–Pugh grading at 6 weeks was not improved by adding EEG, any VER parameter or serum ammonia.

It is concluded that Child–Pugh grading with assessment of encephalopathy using number connection testing is the optimal method for assessment of long-term prognosis 6 weeks after a first variceal haemorrhage in cirrhotic portal hypertension, and recommend this method as routine. Neither neurophysiological testing nor serum ammonia are likely to add to the usefulness of this prognostic assessment, and cannot be recommended for routine use.

ET_A/ET_B endothelin antagonist ameliorates systemic inflammation in a murine model of acute haemorrhagic pancreatitis

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Background The endothelin peptides are multifunctional polykines that have strong constrictor properties in the pancreatic vascular bed. The authors have shown previously that the endothelin antagonist, PD 145065, reduced the local severity of experimental pancreatitis in rats. The effect of endothelin antagonism has not been investigated on the systemic inflammatory response in pancreatitis as measured by serum cytokines in a diet-induced model of acute haemorrhagia pancreatitis in mice

Methods Forty-two female Swiss-Webster mice weighing 18–20 g were divided into four groups. Group 1 ($n = 6$) was fed standard rat chow and treated with PD 145065 20 mg kg^{-1} intraperitoneally every 8 h (controls). Group 2 ($n = 12$) was fed a choline-deficient ethionine-supplemented (CDE) diet and given 100 μl intraperitoneal saline every 8 h. Group 3 ($n = 12$) was fed a CDE diet and treated with PD 145065 20 mg kg^{-1} intraperitoneally every 8 h from initiation of the diet. Group 4 ($n = 12$) was fed a CDE diet and treated with PD 145065 from 48 h after initiation of the diet. Animals were killed at 70 h. Serum was collected for cytokine and amylase measurement. Lung tissue was assessed for myeloperoxidase (MPO) content, a measure of neutrophil extravasation. Pancreases were harvested for histological evaluation.

Results

	Group 1	Group 2	Group 3	Group 4
Lung MPO (units g^{-1})	0·70(0·06)	1·08(0·12)	0·80(0·06)*	0·80(0·05)*
IL-6 (pg ml^{-1})	1·4(1·4)	1 168(360)	326(170)*	1 150(326)
IL-10 (pg ml^{-1})	0	250(152)	112(49)*	105(99)*
Amylase (units l^{-1})	4129(670)	28 279(3407)	19 241(2175)*	15 854(2370)*
Histology score	0	7·3(0·4)	3·9(0·5)*	3·4(0·6)*

Values are mean(s.e.m.) IL, interleukin. $^*P<0·05$ *versus* group 2

Conclusion The endothelin antagonist, PD 145065, decreased the severity of experimental pancreatitis and reduced the levels of markers of systemic inflammation. Late treatment at 48 h failed to prevent the rise in IL-6 but attenuated lung MPO and serum amylase rise. This suggests that endothelin receptor blockade decreases the release of cytokines from systemic macrophages and monocytes and may have a role in the treatment of both the local and systemic manifestations of pancreatitis, even after the onset of the disease.

Changes of macrohaemodynamics, hepatic microcirculation and function in brain-dead organ donors: a new experimental model for analysis of the hepatic microcirculation

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Background The shortage of donor organs has become a central problem in liver transplantation The macrohaemodynamic, hormonal and metabolic impairment of the brain-dead organ donor is often bound with the deterioration of graft viability leading to organ discarding or acceptance of high risk for poor initial graft function Nevertheless, the impact of brain death on the hepatic microcirculation, which has a close relation with graft viability, has not been studied. A novel model for quantitative analysis of the hepatic microcirculation in brain-dead organ donors by means of intravital fluorescence microscopy has been established.

Methods Mechanically ventilated male Sprague–Dawley rats were craniotomized to place an epidural balloon and electrodes for electroencephalography (EEG) and laparotomized for intravital fluorescence microscopy. Mean arterial pressure (MAP), heart rate (HR), bile flow and urine osmolarity were monitored. As parameters of hepatic microcirculation, sinusoidal perfusion, stagnant sinusoidal and adherent postsinusoidal venular leucocytes and the velocity of leucocytes flowing freely in sinusoid and postsinusoidal venules were evaluated quantitatively. In the brain-death group ($n = 6$), brain death was induced through insufflation of the intracranial balloon. The control group ($n = 6$) served as sham controls. The parameters were measured before and until 3 h after induction of brain death.

Results In the brain-death group, EEG showed electrical silence and the absence of a corneal reflex was verified. MAP (baseline mean(s.d.) 107(17) mmHg) and HR (baseline mean(s.d.) 338(36) min^{-1}) were raised significantly within 5 min after induction of brain death (MAP: 181(12) mmHg: HR 411(30) min^{-1}) and decreased to significantly lower level (MAP 63(20) mmHg: HR 327(40) min^{-1}) 3 h after induction of brain death. Urine osmolarity was significantly lower and serum osmolarity was significantly higher. Bile production decreased significantly mean(s.d.) 1·18(0·25) *versus* 1·56(0·26) μl per min per g liver in the control group) Furthermore, a higher number of non-perfused sinusoids (15·7 *versus* 6·2 per cent in control group, $P<0·01$), sinusoidal stagnant and postsinusoidal venular adherent leucocytes (53·9 per lobule and 259 mm^{-2} *versus* 25·2 per lobule and 125 mm^{-2} in control group respectively, $P<0·05$) and decrease in the velocity of freely flowing postsinusoidal venular leucocytes (0·92 *versus* 1·26 mm s^{-1} in control group; $P<0·01$) were documented at 3 h after brain death.

Conclusion A new experimental model was established in the rat which adequately simulates the changes in a haemodynamic and functional parameters in brain-dead organ donors and allows analysis of the hepatic microcirculation under the condition of brain death. These results show for the first time that sinusoidal perfusion is compromised after brain death, possibly through an increased leucocyte activation and accumulation in the hepatic microvasculature This model is suitable for the qualitative and quantitative investigation of the fundamental mechanisms of compromised hepatic function elicited by brain death.

Helicobacter pylori infection: how important is the oral route?

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Background An attempt was made to identify the natural reservoir and the route of transmission of *Helicobacter pylori* infection.

Attenuation of acetaminophen-mediated hepatic injury by taurine

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Background Acetaminophen (ACE) in excessive dose has been shown to cause hepatic injury in both humans and animals. Recent evidence suggests that the oxidative stress response plays a crucial role in the induction of this injury. Since the conditionally essential amino acid taurine has been demonstrated previously to prevent hepatocyte death through inhibition of both nitric oxide and reactive oxygen intermediate production. It was hypothesized that taurine may protect against hepatic damage induced by ACE. The aim of this study was to evaluate the protective effect of taurine on ACE-mediated hepatic injury

Methods Male Sprague–Dawley rats were randomized into three groups: saline (intraperitoneal) as control, ACE (intraperitoneal 800 mg kg^{-1}), and ACE (intraperitoneal, 800 mg kg^{-1}), and ACE (intraperitoneal, 800 mg kg^{-1}) plus taurine (intraperitoneal 200 mg kg^{-1} 12 h before ACE injection) Hepatic damage was evaluated by measuring serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels, as well as histological examination. The induction of apoptosis in the liver was determined by detecting the percentage of DNA fragments using enzyme-linked immunosorbent assay and DNA gel electrophoresis.

	Saline ($n=10$)	ACE ($n=10$)	ACE + taurine ($n=10$)
AST (units ml^{-1})	114(28)	208(93)*	123(31)†
ALT (units ml^{-1})	699(109)	888(154)*	756(108)†
DNA fragments (%)	100(28)	533(93)*	270(59)*†

Values are mean(s.d.) $^*P<0{\cdot}05$ *versus* saline; $P<0{\cdot}05$ *versus* ACE (analysis of variance)

Results Injection of rats with 200 and 400 mg kg^{-1} ACE for 24 h did not cause significant hepatic damage (data not shown). However, ACE at 800 mg kg^{-1} resulted in significant increases in serum AST and ALT levels and hepatic pathological alterations. Rats receiving ACE 800 mg kg^{-1} showed massive production of DNA fragmentation in the liver ($P<0{\cdot}05$ *versus* saline group) Preadministraton of taurine protected rats against subsequent ACE-mediated hepatic injury as represented by a decrease in hepatic enzyme release and the attenuation of induction of DNA fragmentation. Preliminary histological evaluation suggests that the biochemical changes are supported by a decrease in the number of individual necrotic hepatocytes in the taurine-treated group compared with the ACE-treated group.

Conclusion These data indicate that injection of rats with ACE results in apoptosis in the liver. This may be one of the pathways by which ACE causes hepatic injury Prevention of this injury by taurine suggests a prophylactic role for this amino acid in ACE-mediated hepatic injury.

Human liver sinusoidal lymphocytes suppress generation of an allogeneic response: do they contribute to liver graft acceptance?

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Background Liver allografts are more easily accepted than other organ transplants. The mechanism underlying the tolerance is a matter of controversy. There is a large body of evidence suggesting that the donor liver passenger cells are responsible for the evolution of tolerance in the recipient. In the authors' previous studies the existence of liver sinusoidal lymphocytes (LSL) in human liver sinusoids was documented. These cells are not washed out during the liver harvesting procedure but are transferred into the recipients within the graft. The aim of the study was to investigate whether these cells have immunoregulatory function toward allogeneic lymphocytes.

Methods Fragments of liver obtained after partial hepatectomy in 30 patients were perfused at high pressure (50 cm H_2O) with warm (37°C) calcium- and magnesium-free Dulbecco phosphate buffered saline solution with 0·1 per cent ethylene diamine tetra-acetic acid in order to wash out all marginated cells. Mononuclear cells were isolated from peripheral blood and liver lavage by centrifugation on Percoll–Paque density gradients Proliferation of peripheral blood lymphocytes (PBL) from partially hepatectomized patients to phytohaemagglutinin (PHA) in the presence of autologous LSL was measured in 6 days of culture Responsiveness of allogeneic PBL obtained from volunteers to PBL and LSL from hepatectomized patients was investigated Cytokine production by LSL and PBL upon stimulation with interleukin (IL) 2 was estimated in the supernatants after 5 days of culture

Results LSL were poor responders to PHA in comparison to PBL (4673 *versus* 17 443 c.p.m.). The addition of LSL inhibited the responsiveness of autologous PBL to allogeneic PBL (1800 *versus* control 4011 c.p.m.) Moreover, LSL revealed a tendency to lower the allogeneic responsiveness of PBL when added to autologous stimulating PBL (3447 *versus* control 4951 c.p.m). There was no difference in the concentration of immunosuppressive cytokines produced by LSL and PBL: IL-4 (76 *versus* 76 pg ml^{-1}), IL-10 (34 *versus* 36 pg ml^{-1}) and IL-13 (785 *versus* 658 pg ml^{-1})

Conclusion LSL contain a population of highly suppressive cells against allogeneic lymphocytes. These results suggest that allogeneic liver graft tolerance may operate through decreased proliferation of reactive T cells in the recipients because of the presence of donor LSL. The suppressive effect of LSL does not seem to be related to cytokine production

Long-term prognostic significance of tests of encephalopathy in cirrhotic portal hypertension

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Encephalopathy frequently complicates variceal haemorrhage and liver failure. Together with ascites, bilirubin, albumin and prothrombin time, simple clinical scoring of encephalopathy is used to grade patients with increasingly severe liver disease into A, B or C on the Child–Pugh classification, to predict early and long-term survival. A prospective study of detailed clinical and laboratory measures of encephalopathy was conducted to determine their long-term prognostic significance following acute variceal haemorrhage in cirrhotic portal hypertension.

From 1984 to 1993 inclusive, 67 patients underwent detailed investigation 6 weeks after a first variceal bleed, then remained under close follow-up Encepthalopathy was graded clinically as absent, mild or severe, and assessed using a standardized number connection test (none, mild, moderate, severe), electroencephalography (EEG), visual evoked responses (VER; latency, pattern and amplitude) and serum ammonia after 12 h of fasting. Kaplan–Meier plots with log rank testing were used for analysis.

Thirty-six patients died during follow-up. The complications of cirrhosis directly caused 30 of these deaths and were implicated in all others. Child–Pugh grading with crude clinical encephalopathy scoring at 6 weeks predicted survival (A and B *versus* C; $P=0{\cdot}001$). Child–Pugh grading with assessment of

Early prognosis of the level of amputation in cold injury by means of ^{99m}Tc scintigraphy

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Background Frostbite constitutes a pathology for urgent treatment which in the most severe cases inevitably leads to deep necrosis and amputation. However, to locate the exact level of tissue death it is necessary to wait an average of 45 days, which is too long both for the surgeon and the patient, who require rapid and reliable information. With the aim of an early discovery of whether amputation is necessary owing to the frostbite and what extent it will affect, the authors have made a comparative study between gammagraphic images of the affected region and the definitive level of surgical amputation.

Methods A comparative study was made of a total of 101 frostbitten fingers and toes, corresponding to 17 hands (64 fingers) and nine feet (37 toes) of nine patients selected from 88. The gammagraphic study was performed in three phases with the radioisotope ^{99m}Tc during the first, second and third weeks after frostbite. Only the images obtained in the late phase of each examination were used as reference. The parameters evaluated by means of gammagraphy were: (1) the presence of nuclei of hypercaptation of ^{99m}Tc without images of gammagraphic amputation, in theory corresponding to fingers and toes healed 'ad integrum' and (2) the appearance of gammagraphic amputation lines due to isotope detention, in theory corresponding to the surgical amputation These were compared with the following macroscopic parameters: lesions healed without surgical amputation and lesions which required surgical amputation.

Results From the real (macroscopic) perspective, the definitive number of surgical amputations was 42 with 59 healed extremities. From the gammagraphic perspective, in the first week 47 images of gammagraphic amputation appeared with 54 as nuclei of hypercaptation. In the second week 39 images of gammagraphic amputation and 62 nuclei of hypercaptation were observed. In the third week the same results were obtained as in the second week. The difference between gammagraphic images and the real results, either as false positives or false negatives, was always due to lesions (generally apical) of the distal phalanx. The gammagraphic examination of the second week reflected amputation levels which may be superimposed in extension on those observed after surgical amputation, which occurs to a lesser extent with the examination performed during the first week (amputation images more proximal than in reality).

Conclusion The gammagraphic study with ^{99m}Tc of frostbite lesions is an excellent test for the early and reliable determination (first 15 days) of the requirement or not for surgical amputation and its level. Nevertheless, this examination presents an error margin detected in studies carried out during both the first and second week. This error is, however, acceptable in percentage values and, in this study, always corresponded to the anatomically more distal lesion in the extremities (last phalanx).

H_2-receptor antagonists may cause adenocarcinoma of the lower oesophagus and gastric cardia

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Background Adenocarcinoma of the lower oesophagus and gastric cardia has shown a dramatic worldwide increase in incidence over the past 2·5 decades but the cause is unknown. It has been suggested that nonsteroidal anti-inflammatory drugs (NSAIDs) may have a protective effect against carcinoma of the oesophagus but H_2-receptor antagonists may allow achlorhydric reflux to continue without symptoms It is postulated that such asymptomatic reflux is uncontrolled by the usual conservative measures and may lead to increased oesophageal damage. H_2-receptor antagonists were marketed in 1970 and might be the cause of the observed increase of cardio-oesophageal carcinoma (COC).

Methods In a case-control study 56 subjects dying from COC in the period 1 January 1990 to 31 December 1992 were compared with 56 age- and sex-matched controls dying from myocardial infarction. There were 28 women and 84 men of mean age 69 8 years The National Health Service record containing the lifetime prescription history of each subject was retrieved from the health authority. Each prescription was recorded omitting drugs taken in the 2 years immediately before diagnosis. Analysis was performed using conditional logistic regression. Other variables including antacids, steroids, smoking and alcohol were also examined.

Results Subjects dying from COC were more likely to have consumed H_2-receptor antagonists (relative risk (RR) 9 (confidence interval 1·8–46), $P = 0 01$). On the other hand, NSAIDs had a protective effect (RR 0·23 (0·06–0·8), $P = 0·02$).

Conclusion This study supports a protective effect of NSAIDs against COC However, H_2-receptor antagonists appear to have a harmful effect, which may explain the worldwide increase in COC.

Diagnostic minilaparoscopy under local anaesthesia in the management of acute abdominal pain

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Background Between 30 and 50 per cent of emergency admissions to general surgical units in the UK are for acute abdominal pain. Definitive diagnosis based on 'hard' clinical and radiological signs is possible in less than 30 per cent of such cases Therefore in 70 per cent of cases, a policy of 'watch and wait' or 'look and see' is adopted. The former may lead to an unnecessarily prolonged admission and the latter to unnecessary laparotomy or appendicetomy. Laparoscopy would appear to be the ideal technique in assessing patients with acute abdominal pain, but usually requires general anaesthesia. The authors experience with diagnostic laparoscopy under local anaesthesia (LA) using a 2-mm diameter laparoscope is reported.

Methods Thirty patients (11 men), of median age 24 (range 18–49) years, admitted with abdominal pain of uncertain aetiology as assessed by clinical and routine blood investigations were included in the study. Diagnostic minilaparoscopy was performed under LA (maximum 10 ml 1 per cent lignocaine) with supplemental intravenous sedation (midazolam 5 mg maximum), antiemetic (metoclopramide 10 mg) and vagolytic (glycopyrrolate 2 mg) using carbon dioxide to create the pneumoperitoneum. All patients were also connected to an electrocardiographic/pulse oximetry monitor during the procedure. Videolaparoscopy was performed with a 1·98-mm fibreoptic laparoscope and accessory 2-mm graspers and blunt probes (Imagyn Medical/AutoSuture) which were inserted via secondary 2-mm ports.

Results The average length of the procedure was 25 min There were no perioperative or postoperative complications. The procedure was abandoned in one patient because of intractable shoulder pain. In four patients, acute appendicitis was diagnosed and an open appendicectomy was performed. A diagnosis of pelvic inflammatory disease was made in six patients, acute diverticulitis in two, ruptured ovarian cyst in two and non-specific abdominal pain in 15 patients. The average stay in hospital was 2 days. The optical quality of the views was comparable to that obtained with 10-mm laparoscopes.

Conclusion Diagnostic minilaparoscopy under LA is a valuable tool for the assessment of patients with acute abdominal pain. It has the potential of reducing the length of hospital stay and unnecessary laparotomy/appendicectomy in patients with acute abdominal pain.

injury in a dose- and time-dependent manner by intervening a pathomechanisms of the 'reflow paradox' but not of the 'no reflow' phenomenon

CEAP classification in chronic venous disease: haemodynamics in classes 0–6

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Background The new CEAP classification of chronic venous disease (CVD) provides seven clinical classes: class 0, no visible or palpable signs of venous disease but with reflux, class 1, telangiectases and reticular veins, class 2, varicose veins; class 3, swelling; class 4, skin changes; class 5, healed ulcers, and class 6, active ulcers. The aim of the study was to determine the haemodynamic changes associated with each CEAP class.

Methods Some 130 limbs (classes 1–6) of patients with CVD and 20 limbs of volunteers (class 0) were included in the study. The number of limbs per class was as follows class 0, 20; class 1, 23, class 2, 25, class 3, 21; class 4, 21; class 5, 20; and class 6, 20. The groups were matched for age and sex. Patients with previous venous surgery, injection sclerotherapy and arterial disease were excluded. Colour flow dulex imaging was used to identify the presence of CVD and air plethysmography was used to determine venous haemodynamics. The following parameters were measured: amount of reflux (VFI), residual volume fraction (RVF) and ejection fraction of the calf muscle pump. Data analysis was performed using non-parametric statistics (Mann–Whitney *U* test) and linear regression.

Results There was a linear relationship between VFI and clinical classes (Pearson $r = 0{\cdot}6$) Median VFI increased from 0·8 ml^{-1} s^{-1} in class 0 to 2·6, 3·4, 6·4, 6·2 and 8·2 for classes 2–6 respectively ($P < 0{\cdot}0001$) The increase was not statistically significant between classes 0 and 1, and also between classes 4, 5 and 6 RVF increased from 25 per cent in class 0 to 36 and 40 per cent in classes 5 and 6 respectively ($P < 0{\cdot}03$). There was no significant change in ejection fraction between classes

Conclusion The results show that VFI and RVF which is related to the ambulatory venous pressure increase progressively with increasing grade of disease. Limbs with skin changes, healed ulcers and active ulcers appear to be similar haemodynamically The possibility of other factors, such as duration of disease and diligent use of elastic compression influencing progression, merits further investigation

Thermographic assessment of digital vasospasm may provide aetiological clues

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Background Some 20 000 workers in the UK are estimated to suffer from digital artery vasospasm, as part of the hand arm vibration syndrome (HAVS) The diagnosis of HAVS is clinically based, and the need for an objective investigation to support the diagnosis and exclude primary Raynaud's phenomenon (RP) has been highlighted. The potential of cold provocation thermography (CPT) to fulfil this role was analysed

Methods CPT was performed on three groups of patients: eight controls (c) (five men, three women; median age 35 (range 24–78) years), 21 patients with primary RP (five men, 16 women, median age 38 (range 16–76) years) and 21 patients with HAVS (20 men, one woman; median age 45 (range 29–81) years) A precooling thermal image was taken using an infrared camera. Patients then put on closely fitting, thin, latex gloves and immersed their hands in water at a temperature of 5°C for 1 min Following glove removal, further images were taken every 30 s for 10 min Finger tip and base temperatures and the digital temperature gradient were analysed on each digit, on each image.

	Tip			Base			Gradient		
Results	C	Primary RP	HAVS	C	Primary RP	HAVS	C	Primary RP	HAVS
Precooling	34·1	28·8*	30·6*†	34	30*	32*†	−0·1	−0·9*	−1·3*
Time after cooling									
0 min	20·9	19·1*	18·8*	21·4	19·7	20·2*	−0·1	−0·6*	−1·1*†
1·5 min	28	20·4*	20·8*	26·8	23·1*	23·7*	0·4	−2*	−2·9*†
3 min	33·6	21·1*	21·3*	31	23·8*	24·6*†	1·5	−2·6*	−3·2*†
4·5 min	34·5	21·6*	21·6*	33	24·2*	25*†	0·9	−2·6*	−3*
6 min	34·5	21·7*	22·5†	33·6	24·4*	26·5*†	0·7	−2·4*	−2·5*
7·5 min	34·9	22·4*	28*†	34·2	24·5*	27·7*†	0·4	−1·8*	−0·7*
9 min	34·7	23·1*	30·1*†	34·2	24·9*	29*†	0·3	−1·4*	−0·1

Values are median finger temperatures (°C) $^{*}P < 0{\cdot}01$ *versus* C, $P < 0{\cdot}01$ *versus* primary RP (Mann–Whitney *U* test)

Conclusion CPT strongly supports the clinical diagnosis of digital vasospasm Digital temperature gradient and basal temperature in the early and late phases of rewarming respectively seem to be the most promising aetiological indicators.

Does the external carotid artery contribute to cerebral perfusion in carotid disease?

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The contribution of the external carotid artery (ECA) and extra-to-intracranial collaterals to cerebral perfusion has been studied in 77 patients (mean age 68 (range 51–86) years) undergoing carotid surgery. Middle cerebral artery blood flow velocity was measured by transcranial Doppler (TCD), and ipsilateral regional cerebral oxygen saturation (CsO_2) by reflected near infrared spectroscopy. Carotid endarterectomy was performed for greater than 70 per cent internal carotid stenosis. CsO_2 was recorded using a sensor placed in the temporal region over the middle cerebral artery territory (Somanetics, USA) and TCD of the ipsilateral middle cerebral artery was recorded using a temporal window.

	CsO_2 (%)		TCD (cm^{-1} s^{-1})	
	Mean	Mean fall	Mean	Mean % fall
Preclamp	69·8	—	40·8	—
After ECA clamp	66·7	3·1	35·2	12·9
After ICA clamp	62·7	7·6	18·5	51·0

ICA, internal carotid artery

There was a consistent fall in both CsO_2 and middle cerebral artery flow on ECA cross-clamping with a further and greater fall on ICA clamping. Previous studies have shown that a fall measured by TCD of 8 per cent is equivalent to a 1 per cent fall in CsO_2, in this study the results were similar with a ratio of fall in TCD to fall in CsO_2 of 4·2 on ECA clamping and 6·7 on ICA clamping

On clamping the ipsilateral ECA in patients with carotid disease, the decreases in both CsO_2 and middle cerebral artery flow velocity are equivalent in terms of reduced perfusion of the relevant cerebral hemisphere. The extracranial circulation therefore makes a significant contribution to intracranial blood flow and oxygen saturation in patients with significant carotid stenosis better predictor of death and could be used to compare vascular units, and present important information to purchasers and providers of health care.

Relationship between the performance of carotid endarterectomy and incidence of transient ischaemic attack and stroke

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Background The relationship between the rate of carotid endarterectomy (CEA) and incidence of transient ischaemic attack (TIA) and stroke was examined on a national and regional level.

Methods National and regional rates of CEA, incidence of TIA and ischaemic stroke, and changes in regional population with respect to age were assessed using routine data sources. A computerized database of 402 representative general practices covering 4 million patients across the UK between 1992 and 1995 was used.

Results There was a national increase in the rate of CEA by a factor of 1·7 for England, 3 for Scotland and 2·2 for Northern Ireland between 1992 and 1995. The increase across English Regional Health Authorities (RHAs) There was no significant change in the incidence of TIA and stroke in the RHAs over the time period. The mean TIA and stroke rate was 292 per 100 000 and 356 per 100 000 per annum respectively. There was a 2·5-fold difference in the incidence of cerebrovascular disease between the RHAs. The inter-regional ratios of CEA per 1000 TIAs and 1000 strokes ranged ten to 32 and seven to 22 respectively in 1995. There was no correlation between regional incidence of cerebrovascular disease and regional rate of CEA.

Conclusion There has been an increased rate of CEA in all three countries between 1992 and 1995. The incidence of cerebrovascular disease in the population may be higher than previously recognized. There is a large inter-regional variation in performance of CEA which is not commensurate with the inter-regional variation in incidence of cerebrovascular disease. Equitable distribution of resources is needed to ensure provision of vascular services where most needed.

Influence of carotid endarterectomy on cognitive function

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Subtle changes in cognitive function are more common than stroke in patients undergoing carotid endarterectomy (CE) These changes were investigated in relation to preoperative cerebrovascular reactivity (CVR) to inhaled carbon dioxide in patients undergoing CE. CE was performed on 37 patients with a mean age of 68 (53–82) years for symptomatic greater than 70 per cent stenosis of the internal carotid artery. Twelve patients with normal CVR and 25 with impaired CVR were examined before and at 1 and 8 weeks after CE using the Cognitive Drug Research computerized assessment system, a validated battery of tests. Patients had to respond to visual stimuli by pressing a yes/no button.

Overall, there was an improvement in memory tasks at 8 weeks following CE compared with preoperative scores ($P=0·04$) Initially patients with impaired CVR performed less well on all tasks. When retested at 1 week after operation, the patients with impaired CVR showed greater declines on most tasks compared with those with normal CVR (e.g. picture recognition accuracy $P<0·04$). Patients with impaired CVR had poorer cognitive function before operation compared with normals, which deteriorated further by 1 week after operation. However, by 8 weeks CE had improved cognition irrespective of pre-existing CVR.

Reduction of microvascular postischaemic reperfusion injury in striated muscle of the hamster by intravenous prostaglandins E_1 and I_2

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Background Microcirculatory analysis and specific therapeutic intervention play a pivotal role in counteracting complications due to ischaemia-reperfusion injury. Failure of capillary perfusion (no reflow) and reoxygenation-associated (reflow paradox) mechanisms such as leucocyte-endothelium interaction, release of toxic mediators (oxygen-derived free radicals, leukotrienes, platelet-activating factor) and subsequent increase of vascular permeability are proposed to represent the pathomechanisms of microvascular postischaemic injury. Experimental studies have demonstrated cytoprotective effects of prostaglandin E_1 (PGE_1) and I_2 (PGI_2) with inhibition of postischaemic injury. The aim of this study was to investigate and analyse quantitatively the effect of PGE_1 and PGI_2, independent of their vasoactive effects, on microvascular reperfusion–injury of striated muscle.

Methods Under pentobarbital sodium anaesthesia (60 mg per kg body-weight intraperitoneally) a titanium skinfold chamber, and jugular vein and carotid artery catheters were implanted in Syrian golden hamsters. With the use of *in vivo* microscopy the microcirculation of the striated skin muscle was analysed quantitatively. Leucocyte-endothelium interaction was determined after *in vivo* staining of leucocytes with rhodamin 6G (0·1 µmol per kg body-weight intravenously), microvascular endothelial permeability and functional capillary density were assessed after injection of FITC-labelled dextran (0·2 ml M_r intravenously, 150 000). The microcirculatory parameters were analysed before 4 h of pressure-induced ischaemia, and 0 5, 2 and 24 h after onset of reperfusion PGE_1 (1 µg per kg body-weight per min intravenously; Prostavasin) and PGI_2 (250 ng per kg body-weight per min intravenously; Epoprostenol) were administered in doses known to not exert macrohaemodynamic and microhaemodynamic effects by constant infusion (0·17 ml h^{-1}) for a 2-h short-term (PGE_1. $n=8$; PGI_2: $n=8$) or 6-h long-term (PGE_1: $n=7$, PGI_2: $n=7$) period (starting 5 min before reperfusion or 5 min before ischaemia respectively). The control groups were assessed during 6-h long-term infusion (starting 5 min before the 4-h ischaemia) of PGE_1 ($n=7$) and PGI_2 ($n=6$) vehicle substances. Results are analysed by Wilcoxon test and Mann–Whitney *U* test.

Results In both control groups reperfusion after 4 h of ischaemia caused significant reduction ($P<0·05$) of capillary perfusion rate and marked enhancement ($P<0·05$) of leucocyte rolling and sticking in postcapillary venules with enhanced macromolecular leakage in both arterioles and venules ($P<0·05$) There was no significant difference between the control groups. The 2-h-short-term infusion of PGE_1, but not PGI_2, significantly reduced leucocyte sticking ($P<0·05$) and macromolecular leakage in venules ($P<0·05$) during early reperfusion (0·5–2 h) as well as leakage in arterioles ($P<0·05$) after 24 h of reperfusion. The 6-h long-term infusion of PGI_2 resulted in a significant reduction in leucocyte adherence 0·5 h after reperfusion ($P<0·05$), while microvascular permeability was not influenced. In contrast, PGE_1 long-term infusion revealed no beneficial effects on manifestation of ischaemia–reperfusion injury. Both substances were unable to prevent the postischaemic failure of capillary perfusion.

Conclusion These data confirm that microvascular manifestation of ischaemia–reperfusion injury is characterized by impaired capillary perfusion and stimulation of leucocyte–endothelium interaction with subsequent increase of microvascular permeability. PGE_1 and PGI_2 reduce microvascular reperfusion (range 1–67) months Eleven patients (22 per cent) underwent salvage surgery, 44 (86 per cent) received radiotherapy and 25 (49 per cent) received chemotherapy. Five patients (10 per cent) received all three treatment modalities and 15 (29 per cent) received radiotherapy and chemotherapy. The median hospital cost per patient was £6400 (range £73–47 776).

These data show that patients with recurrent rectal cancer survive longer than expected and require multimodal therapy for palliation This has significant resource implications. Optimal surgery and adjuvant therapy may reduce the severe morbidity from recurrence and in addition have significant financial benefits.

NRAMP gene is associated with Crohn's disease

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Background The natural resistance-associated macrophage protein (*NRAMP*) functions in macrophage regulation especially in the resistance and susceptibility to intracellular pathogens. Because macrophage hyperactivity to intestinal flora has been implicated in the pathogenesis of inflammatory bowel disease (IBD) it was hypothesized that genetic differences of the *NRAMP* gene are associated with IBD.

Methods Two DNA markers near *NRAMP* (D2S1323 and D2S434) were investigated with DNA from 167 unrelated patients (77 with Crohn's disease, 44 with ulcerative colitis and 46 individuals without intestinal disease). Alleles, genotypes and haplotypes were determined after polyacrylamide gel electrophoresis of ^{32}P-radiolabelled polymerase chain reaction products and analysed by χ^2 and Fisher's exact tests. The association between single haplotypes and disease was compared by odds ratio

Results Allele frequencies of D2S1323 (two alleles) and D2S434 (seven alleles) were not different between the groups. Genotype and haplotype frequencies were different between Crohn's disease and control groups ($P = 0·009$, and $P = 0·004$ respectively). Significant associations for the haplotypes *DA*, *BA* and *AB* are shown below

Haplotype	No *	Odds ratio†	*P*
DA			
Controls	24 (25)	—	—
Crohn's disease	19 (12)	0·4 (0·2–0·8)	0·01
Ulcerative colitis	17 (19)	0·8 (0·4–1·6)	0·37
BA			
Controls	4 (4)	—	—
Crohn's disease	19 (12)	3·1 (1·00–9·4)	0·06
Ulcerative colitis	8 (9)	2·2 (0·6–7·6)	0·33
AB			
Controls	0 (0)	—	—
Crohn' disease	8 (5)	n a	0·06
Ulcerative colitis	0 (0)	n a.	n.a.

Values in parentheses are *percentages or †95 per cent confidence intervals. n.a., Not applicable (O haplotypes)

Conclusion These results indicate a novel association between the *NRAMP* gene and Crohn's disease. We believe this is a major advance in determining the aetiology of Crohn's disease.

Early sympathectomy for chronic regional pain syndrome

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Background Chronic regional pain syndrome (CRPS) – previously termed causalgia and reflex sympathetic dystrophy – is a debilitating condition consequent to a noxious event. Whilst there are various non-surgical therapeutic options, sympathectomy is widely recognized as having the most effective and enduring therapeutic effect. The role of early sympathectomy for CRPS was evaluated prospectively in 17 patients.

Methods During a 42-month period (March 1993 – September 1996), 17 patients with CRPS referred by the Addington Hospital Pain Clinic for upper limb sympathectomy were studied Sympathectomy was indicated on the basis of successful sympathetic block or clinical presentation. There were 13 men and four women and the mean age was 32 (23–64) years. The patients were divided into two groups. Group I patients had symptoms present for less than 3 months ($n = 10$) and group II patients had symptoms present for more than 3 months ($n = 7$) A thoracoscopic T2 ganglionectomy (TS) was always attempted. Outcome was assessed subjectively by patients as being excellent, good, fair or poor (unchanged) compared with the preoperative state.

Results Seventeen sympathectomies were performed successfully. In Group 1, six patients underwent a single sympathetic block before surgery and four patients were referred in clinical presentation alone. TS was successful in all group 1 patients. The outcome was excellent in eight patients and good in two Mean follow-up was 26 (range 3–38) months. Group II patients underwent several regional blocks (mean 3·5 (range 3–4)) before surgery. TS was feasible in two patients The outcome was excellent in one and good in one In the remaining five patients, TS could not be performed because of dense pleural adhesions and open sympathectomy (OS) was undertaken. The outcome was excellent in one, good in two and poor in two patients. Complications following OS included Horner's syndrome ($n = 1$) and wound haematoma ($n = 1$) Mean follow-up was 25 (range 2–40) months. No complications of TS were noted in either group.

Conclusion Early TS is an effective and safe procedure for CRPS. Repeated sympathetic block comprises the thoracoscopic route and may influence the beneficial effect of sympathectomy.

Predicting outcome in vascular surgery: how good is POSSUM?

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Background In today's climate of health care reforms, purchasing is increasingly driven by the analysis of outcome. Simple comparative audit has its limitations, notably the failure to assess case mix in vascular practice. Physiological, Operative Scoring System enUeration of Mortality (POSSUM) has been used to overcome some of these problems The accuracy of POSSUM (P) and Portsmouth modified POSSUM (PMP) in predicting the mortality and morbidity rate of vascular operations was assessed.

Methods Some 262 consecutive operations (85 for aortic aneurysm (AA) (56 ruptured); 47 carotid endarterectomies (CE); 70 femoropopliteal (FP) and 60 femorodistal (FD) bypasses) were scored prospectively for P and PMP values (median patient age 72 (interquartile range 65–71) years; 173 men). The observed and predicted mortality and morbidity rates were compared by χ^2 analysis.

Results

	Overall	AA	CE	FP	FD
Observed mortality rate (%)	14	26	2	7	12
P mortality rate (%)	24*	39*	10*	18*	22*
PMP mortality rate (%)	13	24	3	7	14
Observed morbidity rate (%)	74	85	36	58	66
P morbidity rate (%)	65	80	43	58	60

$P < 0·05$ *versus* observed value

Conclusion POSSUM is a good predictor of morbidity in vascular surgical procedures. The PMP score appears to be a

Telomerase activity in adenomatous polyps and carcinoma of the colon

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Background Telomerase is an enzyme which has been identified in germ cells and several tumours. It is not expressed by normal somatic tissues. Telomerase expression enables cells to divide indefinitely and renders them immortal. This immortalization may be an important step in the malignant process. The aim of this study was to determine the incidence of telomerase expression in colorectal cancers and adenomatous polyps and to identify the stage at which the enzyme is first activated. The degree of telomerase activity in polyps was also analysed and correlated with the degree of dysplasia

Methods Telomerase activity was detected using a polymerase chain reaction based technique. Quantitation was done by densitometry.

Results Some 48 of 50 cancers (96 per cent) were found to be positive for telomerase. These ranged from Dukes A lesions to metastatic tumours. Fifty corresponding samples of normal mucosa were negative. Five of 35 polyps were found to be telomerase positive. All five were villous adenomas. The degree of activity increased with degree of dysplasia.

Conclusion Telomerase is expressed early in the malignant process in colorectal cancer. Enzyme activation appears to occur at the dysplastic polyp stage. It is very tumour specific and no significant activity was detected in any of the normal samples analysed Telomerase may be a useful marker for early diagnosis or follow-up of malignant disease. It is also a potential target for drug therapy.

Double-blind randomized trial of 105AD7 vaccine in advanced colorectal cancer

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105AD7 vaccine is a human anti-idiotypic antibody which mimics the tumour-associated antigen 791 Tgp 72. The vaccine has been administered to over 150 patients with no associated toxicity. T-cell responses were observed in 80 per cent of the patients in a phase I trial. The immune responses are exemplified by antigen-specific blastogenesis, interleukin 2 production, enhanced autologous tumour killing, enhanced natural killer activity and tumour infiltration of CD8, CD4 and CD56 cells.

The mechanism of action of the vaccine has been clarified recently. The anti-idiotypic is rapidly internalized on antibody presenting cells by Fc-mediated endocytosis as both Fab and antibody complexed to alum are processed and presented 1000-fold less efficiently than whole antibody. Sequencing of the antibody has revealed that the CDR-H3 is hypermutated and contains human leucocyte antigen (HLA) A1, A3 and A24, and HLA-DR1, 3 and 7 major histocompatibility complex binding motifs. All patients showing T-cell responses had the predicted phenotypes.

In the phase I study patients with advanced colorectal cancer survived significantly longer than contemporary patients. As these patients also exhibited good immune responses, the vaccine has been evaluated in a double- blind randomized phase II trial. Some 165 patients with either liver metastases or local recurrent colorectal cancer have been immunized with either 10 μg 105AD7 by intradermal injection followed by an intramuscular injection of 100 μg 105AD7 alum, or 10 μg saline followed by an intramuscular injection of alum alone. Patients could receive three courses of injections at 6-weekly intervals; 55 per cent of patients completed all three courses, 20 per cent only two and 25 per cent received only a single immunization. There was no antibody-related toxicity in any patient. The final patient was recruited in October 1996 and 31 patients remain alive. Survival is the primary endpoint of this study and final results will be presented at this meeting.

Differential expression of chromosome 11 mucin genes in colorectal cancer

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The mucin genes *MUC2* and *MUC5AC* have been localized to chromosome 11. The authors have recently demonstrated differential expression of these genes in adenomas using *in situ* hybridization and immunohistochemistry. This observation has been extended to probe for the mature gene product of these genes in epithelial cell adenocarcinoma of the rectum and in the associated transitional zone (TZ).

Seventeen adenocarcinomas of the rectum were studied. The mature mucin gene product was detected immunohistochemically using recently developed anti-*MUC2* and anti-*MUC5AC* polyclonal antibodies. The tumour, TZ and normal mucosa were scored separately on a scale of 0–4.

MUC5AC protein product is not expressed in normal rectal mucosa. There is *de novo* expression of *MUC5AC* in rectal adenocarcinoma and its associated TZ compared with normal mucosa (tumour 1 (0–3 ($P<0·003$), TZ 1 (0–1) ($P<0·005$). The level of the gene product was higher in the cancers than in the TZ ($P<0·04$). There was no consistent change in the expression of *MUC2*.

For the first time, *De novo* expression of the *MUC5AC* gene has been demonstrated in epithelial colorectal cancers. In tumours positive for this product, there is a graded increase from the associated TZ and normal mucosa. There is differential expression of *MUC2* and *MUC5AC* in adenocarcinoma of the rectum.

Health economics and clinical implications of recurrent rectal cancer

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There are over 10 000 new cases of rectal cancer per year in the UK and the incidence of local recurrence following surgery ranges from 3 per cent to over 20 per cent. This group represents a significant therapeutic and financial drain on the national health resource.

Some 51 patients referred between 1990 and 1994 with a diagnosis of recurrent rectal cancer have been reviewed retrospectively. All patients had undergone curative surgery and had histologically clear distal, lateral and proximal margins. The data were collected on the diagnosis and management of recurrent disease, and the hospital costs were estimated by assessing major interventions including surgery, radiotherapy and chemotherapy, outpatient visits and inpatient days, and imaging procedures performed on each patient during their management.

The mean(s.d.) age of patients at primary surgery was 69(12) years. Some 26 patients (51 per cent) underwent anterior resection, 20 (39 per cent) abdominoperineal resection, four (8 per cent) Hartmann's procedure and one (2 per cent) endoanal excision There were four (8 per cent) Dukes A, 14 (27 per cent) B and 22 (65 per cent) Dukes C lesions. Nine patients had received adjuvant therapy. The median time to recurrence was 14 (range 2–60) months with 33 patients (65 per cent) suffering local recurrence, 13 (25 per cent) with distant spread and five (10 per cent) with both. Median survival following recurrence was 9

These results suggest that tumour enhancement of angiogenesis occurs by increased initiation of the angiogenic response and also suggests that subsequent vessel growth rates are tumour-independent It is predicted that effective antiangiogenic therapies will block the tumour's ability to augment angiogenesis initiation

Vascular endothelial growth factor in premenopausal women: indicator of the best time for breast cancer surgery?

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The controversy regarding breast cancer prognosis and timing of primary surgery is well known. The differing outcome may be due to cyclical variation in secretion of angiogenic cytokines, the most potent of which is vascular endothelial growth factor (VEGF). In this study the variation of serum VEGF with the menstrual cycle was assessed prospectively in 14 normal premenopausal women. Three postmenopausal women were included as controls.

Blood samples were taken at 4-day intervals throughout the cycle VEGF, follicle-stimulating (FSH), leutinizing hormone (LH) and progesterone were measured by enzyme-linked immunosorbent assay and oestradiol by radioimmunoassay Cycles were divided into follicular and luteal phases on the basis of an LH surge and an appropriate progesterone response. Statistical analysis was by Mann–Whitney *U* test and Spearman's correlation. Values are median (interquartile range).

VEGF levels were significantly lower in the luteal phase compared with the follicular phase (174·7 (83·1–239·8) *versus* 206·5 (119·9–327·7) pg ml^{-1}, $P = 0{\cdot}03$) in premenopausal women There was a corresponding increase in luteal phase progesterone (18·8 (3·4–32·8) *versus* 0·8 (0·6–1·6) nmol l^{-1}; $P < 0{\cdot}0005$) A significant negative correlation existed between VEGF and progesterone (rho $= -0{\cdot}193$, $P = 0{\cdot}03$). Postmenopausal VEGF levels did not vary appreciably with time 417·9 (389·7–423·4) pg ml^{-1})

This study provides compelling evidence that the increased progesterone levels of the luteal phase reduce VEGF levels This has major implications for the timing of surgery in premenopausal women with breast cancer

Antioestrogens and angiogenesis on the chick chorioallantoic membrane

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Background Angiogenesis requires matrix protein remodelling, endothelial cell multiplication, migration and differentiation Oestrogens are intimately involved in each of these steps but there is considerable redundancy amongst angiogenic pathways and crosstalk between their secondary messengers The successful use of the chick chorioallantoic membrane angiogenesis bioassay with human breast carcinoma cell lines EMCF7 oestrogen receptor positive and MDA231 oestrogen receptor negative is reported.

Methods Using stereoscopic microscopy blood vessels invading a 20-µl collagen gel were counted through a 2 × 2 mm nylon mesh over 10 days. MDA231s and EMCF7s in gels were placed on the mesh and the effects of tamoxifen or AGM182 780 (a pure antioestrogen) added to the gels were studied Results are expressed as a percentage of mesh squares containing blood vessels. Substance P was used as a positive control.

Results Both cell lines were angiogenic. The MDA231s (mean 74 per cent) were more angiogenic than the EMCF7s (mean 16 per cent) ($P = 0{\cdot}0019$, Mann–Whitney *U* test). The angiostatic effects of tamoxifen (3 per cent) over positive controls (90 per cent) were confirmed ($P = 0{\cdot}0005$) but AGM182 780 (64 per cent) was not significant over controls (68 per cent) both at 100 µg per gel Tamoxifen at 25 µg, 50 µg and 75 µg per gel was unable to suppress significantly the angiogenic response of either cell line. In the presence of low concentrations of tamoxifen (25 µg per gel) (8 per cent) the angiogenic response of the oestrogen receptor positive cell line EMCF7 was transiently depressed compared with negative controls (22 per cent) ($P = 0{\cdot}05$).

Conclusion Tamoxifen was angiostatic in the *in vivo* assay but its effects were eventually overcome by other angiogenic stimuli produced both by EMCF7s and MDA231s Tamoxifen's antiangiogenic activity is probably not due to its partial oestrogen antagonism although oestrogens are probably permissive to other factors stimulating pathogenic neovascularization. This model could prove useful in assessing multiple angiogenic pathway blockade supplementing tamoxifen with angiostatic agents.

Morphological adaptation in the ileoanal pouch is not associated with a change in the supramucosal barrier

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The formation of an ileoanal pouch (IAP) can be associated with a defined morphological adaptation from ileal to colonic type mucosa, raising the possibility of an increased dysplastic potential within the reservoir. The physiological characteristics of the supramucosal defence barrier have been studied and biological alterations correlated with morphological adaptation. Fifty-one patients with an IAP and 39 controls (ileal $n = 16$; colonic $n = 23$) were studied. Paired mucosal biopsies from 31 W and J pouches and the controls were established in organ culture for 24 h with radioactive mucin precursors [^{35}S]sulphate and [^{3}H]glucosamine. A third biopsy was stained with haematoxylin and eosin and assigned an inflammatory score (IS). The secreted and cellular fractions were purified by gel filtration and the median ratio of incorporation of the precursors (^{35}S/^{3}H) was used as a measure of sulphation. Total mucin produced was determined by Western blotting with wheatgerm agglutinin followed by densitometry. Mucin precursor turnover (counts per µg of DNA) and total mucin µg per µg of DNA) was expressed as a ratio of the total DNA content (measured by fluorocytometry)

The median (range) sulphation ratios in the ileal secreted and cellular fractions were low (0·28 (0·01–1·98) and 0·35 (0·13–1·03)) compared with those of the highly sulphated colonic biopsies (1·16 (0·55–3·20) and 1·75 (0·49–3·30)) ($P < 0{\cdot}002$). Sulphate, glucosamine and total mucin turnover was unaltered. The secreted and cellular fractions from both the W (0·31 (0·01–0·88) and 0·37 (0·06–0·67)) and J (0·44 (0·03–0·97) and 0·49 (0·11–1·42)) reservoirs were distinct from highly-sulphated colonic mucin ($P < 0{\cdot}001$) but remained similar to poorly sulphated ileal mucin. The IS was increased in reservoirs with partial villous flattening compared with those that remained villous; 2 (1–5) *versus* 1 (0–4) ($P < 0{\cdot}002$). Adaptation from villous to partial villous was associated with increased sulphation in the secreted fraction (0·28 (0·03–1·29) *versus* 0·36 (0·07–1·06), $P < 0{\cdot}02$) but this remained ileal in nature.

Morphological adaptation in the IAP is not accompanied by a change in the physiological characteristics of the supramucosal defence barrier, so IAP formation may not be associated with an increased risk of dysplasia

$P<0\cdot0001$). By immunocytochemistry, PAI-1 was located principally in malignant cells with few stromal cells staining positive. By Northern blot analysis, PAI-1 messenger RNA (mRNA) was detected in 28 per cent of primary breast cancers. There was no correlation between PAI-1 mRNA and levels of transcript for uPA, tPA, uPA receptor or PAI-2. PAI-1 mRNA correlated significantly with levels of PAI-1 protein ($r=0\cdot318$, $P=0\cdot0391$).

Conclusion PAI-1 like uPA is a strong and independent prognostic marker in breast cancer. These proteins are potential therapeutic targets.

Matrix metalloproteinase activity in breast cancer

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Matrix metalloproteinases (MMPs) are involved in the degradation of extracellular matrix components in tumour invasion and metastasis. Under normal conditions MMPs are tightly regulated, by their activity and specific tissue inhibitors of metalloproteinases, TIMPs. Therefore it is the presence of 'free' active MMPs that is important in tissue degradation.

MMP activity in cell lysates from breast tumours ($n=47$), the surrounding background tissue ($n=37$), normal tissue from breast reductions ($n=7$) and the breast cancer cell line MCF-7 ($n=6$) was determined by quenched fluorescent substrate analysis. The substrate Mca-Pro-Gly-Leu-Dpa-Ala-Arg-NH_2 contains a highly fluorescent 7-methoxycoumarin group (Mca). This substrate is cleaved by all secreted MMPs at the Gly–Leu bond, releasing the coumarin group allowing it to fluoresce. Each sample was incubated with this substrate for 3 h at 37°C. The rate of substrate hydrolysis (RSH), i.e. fluorescence, was determined in picomoles per minute using a fluorimeter connected to computerized software.

	Tumour	Background	Normal	MCF-7
Rate of hydrolysis (pmol min^{-1})	808 (0–8235)	225 (0–6325)*	279 (6–2763)	150 (82–622)

Values are median (range). *$P<0\cdot01$ (analysis of variance, Mann–Whitney *U* test)

The RSH was greater ($P<0\cdot01$) for tumour tissue than the corresponding background, whereas the RSH was similar for background and normal tissue, suggesting that the background behaved 'normally'. The low metastatic cell line MCF-7 also had lower activity than breast tumour. In 86 per cent of the paired tumour and background samples the RSH was greater in tumours. The increased amount of free active MMP in breast tumours may be important in invasion and metastasis.

Active immunization using dendritic cells mixed with tumour cells inhibits the growth of breast cancer

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Dendritic cells (DC) are potent antigen presenting cells and are regarded as crucial for the priming of an immune response. The aim of this study was to test whether bone marrow generated DC are capable of inducing protective immunity against a murine breast cancer (4T1). DC were grown from Balb/c mice by culturing lymphocyte-immunodepleted bone marrow in media containing murine granulocyte–macrophage–colony stimulating factor for 10 days. Balb/c mice (5–8 per group) were immunized intradermally with 1×10^6 DC mixed with 2×10^6 lethally irradiated 4T1 cells on day 0. Mice in control groups were given intradermal inoculations of phosphate buffered saline (PBS), 1×10^6 lethally irradiated 4T1 cells alone. Booster intraperitoneal immunizations of 2×10^6 lethally irradiated 4T1 cells were given on days 7 and 14. Mice were challanged with 5×10^3 4T1 cells subcutaneously 7 days after final immunization. Animals were examined daily and tumour volume recorded twice weekly using calipers. Tumour growth at 21 days is shown below.

Vaccination group	Mean tumour volume (mm^3)
PBS	374(27)
4T1	348(30)
DC	296(32)
DC and 4T1	143(15)

Values are mean(s.e.)

There was a significant reduction in tumour growth of mice immunized with DC mixed with irradiated 4T1 cells compared with other control groups ($P<0\cdot0005$ Kruskal–Wallis test).

These results suggest that DC mixed with tumour cells as a source of undefined tumour antigen can induce an effective anti-tumour immune response. This finding provides a rationale for the use of cultured DC in immunotherapy of breast and other cancers.

T-47D Breast cancer cells enhance initiation of *in vitro* human angiogenesis without accelerating neovessel growth

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Recurrence and mortality rates in patients with breast cancer correlate with the degree of tumour angiogenesis (angiogenic index) The authors have developed a novel *in vitro* human placental vein angiogenesis model (HPVAM) in which discs of fresh placental vein are incorporated into a three-dimensional matrix containing 0·3 per cent fibrin, Medium 199 and 20 per cent fetal bovine serum. These discs initiate an angiogenic response and exhibit linear radial capillary growth in culture. It was hypothesized that the addition of human breast cancer cells to the HPVAM would enhance the incidence of angiogenesis and accelerate the rate of neovessel growth. To test this hypothesis, human vein explants from six placentas were overlaid with medium, with or without $1\cdot5\times10^5$ T-47D human breast cancer cells. Significance was determined by Students' *t* test.

The proportion of discs exhibiting neovessel growth (initiation) by day 12 was significantly increased by the addition of tumour cells.

	Incidence of angiogenesis (%)		
	Day 9	Day 12	Day 15
20% FBS control	20·0	27·8	31·5
20% FBS + T-47D	23·6	38·1	49·6
Percentage increase *versus* control	+18·0	+37·1	+57·5
P*	n.s.	$<0\cdot05$	$<0\cdot001$

$n=165$ at all time points. *Student's *t* test

No statistical difference was seen in mean(s.d.) rates of neovessel growth over 3 days: control 0·13(0·09) mm day^{-1} ($n=22$); T-47D 0·13(0·09) mm day^{-1} ($n=29$).

on 17 patients, 12 months on 35 patients and 6 months on 23 patients, with a median follow-up of 10 months. Secondary surgical intervention was required in 12 of 118 patients (10 per cent). Of those 103 patients who survived beyond 30 days of the procedure another 14 patients (14 per cent) died subsequently. Of these 14 deaths 12 occurred in patients who had been deemed at high surgical risk. The cause of death was myocardial infarction in three, renal failure in two, dialysis line sepsis in two, pneumonia in two, stroke in one and metastatic pancreatic carcinoma in one. Of these late deaths, two followed secondary surgical intervention and the other 12 deaths occurred in the presence of a satisfactory endovascular repair. Significant displacement of the proximal stent occurred in seven of 118 cases (6 per cent). All stent displacements occurred with one variety of repair (unitary bifurcated). Endoleaks on follow-up computed tomography were present in 14 patients, nine from the lumbar vessels, two around the proximal stent, two around the distant stent and one around the iliac occlusion device.

A high mortality rate during follow-up was seen in patients deemed at high risk or unfit for open surgery. An effective aneurysm exclusion may not necessarily prolong survival in this group of patients and a randomized trial is required to define the role of endovascular repair in patients at high surgical risk. An unacceptably high late failure rate is seen with the unitary (Chuter-Gianturco) bifurcated graft.

Assessment of the slope of the end-systolic pressure–volume relationship in rats by the single beat estimation method

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The concept of the end-systolic pressure–volume relationship (ESPVR) is frequently used as a relative load-independent measure of myocardial contractility in large animals and humans. Since no established method exists for the assessment of intraventricular volumes in small animals *in situ*, the end-systolic concept could not be used in these settings. The aim of the study was to establish and validate a new technique to estimate the slope of the ESPVR (Ees) from a single ejecting beat without knowing absolute interventricular volumes.

In 62 anaesthetized rats Ees was calculated from the simultaneously measured left ventricular pressure (Millar-tip manometer) and stroke volume (SV; electromagnetic flow meter) of a single analysed beat ('single beat estimation'): Ees = (Pmax − Pes)/SV, where Pes is end-systolic pressure and Pmax the calculated maximal isovolumetric pressure at the end-diastolic pressure (LVEDP) of the analysed beat. Pmax was estimated by fitting a theoretical isovolumetric pressure curve on the isovolumetric phases of contraction and relaxation (P(t)) of the analysed beat with a non-least square fitting procedure: $P(t) = 0{\cdot}5\ \mathrm{Pmax}\ \cos(\omega + c) + \mathrm{LVEDP}$. Calculated Ees was compared with Ees measured during vena caval occlusion. Left ventricular end-systolic volume (ESV) was calculated as end-diastolic volume (EDV) minus SV, where EDV was estimated from post-mortem LVEDP–EDV curves and LVEDP measured *in situ*. The influence of preload (volume infusion), afterload (aortic constriction) and inotropy (Dobutamine $5\,\mu g\,kg^{-1}$ and verapamil $0{\cdot}3\ mg\,kg^{-1}$) was investigated in random order.

There was a good correlation between measured and calculated Ees at control ($r = 0{\cdot}88$), altered preload ($r = 0{\cdot}84$), afterload ($r = 0{\cdot}89$) and inotropic states ($r = 0{\cdot}92$ under dobutamine, ($r = 0{\cdot}79$) under verapamil). While contractility indices such as Pmax and dP/dtmax showed a clear load dependency, Ees did not change significantly under altered preload and afterload. In contrast a significant increase is mean(s.d.) Ees by dobutamine (+ 45(7 per cent, $P < 0{\cdot}01$) and decrease by verapamil (− 37(5) per cent, $P < 0{,}01$) could be observed.

This new single beat estimation method allows for the first time the assessment of the slope of the ESPVR, a load-independent index of contractility, in small animals without knowing absolute intraventricular volumes.

Abdominal aortic aneurysm size: implications for the feasibility of endovascular repair

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Background The length, width and angulation of the proximal aortic neck and the diameter and tortuosity of the common iliac arteries (CIAs) are important anatomical features which determine whether endovascular repair of an abdominal aortic aneurysm (AAA) is feasible. If unfavourable features were found to be less common in patients with small aneurysms this might have implications for both screening programmes and the timing of endovascular surgery. The aim of this study was to examine the relationship between AAA size and these variables.

Methods Some 215 patients with AAA were assessed with spiral computed tomographic angiography. Computerized multiplanar reconstructions were used to measure proximal neck length, diameter and angulation, both CIA diameters and maximal CIA angulation. The feasibility of endovascular repair for each aneurysm was determined prospectively by guidelines described previously. Patients with small (3·5–5·5 cm, $n67$), medium (5·6–6·7 cm, $n = 77$) and large (greater than 6·8 cm, $n = 71$) aneurysms were compared using the χ^2 test.

Results Large aneurysm size was significantly associated with a proximal neck diameter of more than 3 cm ($P < 0{\cdot}05$), proximal neck angulation greater than 80° ($P < 0{\cdot}001$), CIA diameter above 2·0 cm ($P < 0{\cdot}01$) and CIA tortuosity greater than 90° ($P < 0{\cdot}05$). Only proximal neck angulation differed significantly between small and medium-sized aneurysms ($P < 0{\cdot}01$). The proportion of patients in whom endovascular repair was feasible was significantly lower in the large aneurysm group (42 per cent) than in the small (55 per cent) and medium (57 per cent) groups ($P < 0{\cdot}05$).

Conclusion Patients with aneurysms of diameter 6·8 cm or more have a higher incidence of unfavourable proximal aortic necks and CIAs than those with aneurysms smaller than 6·8 cm, and endovascular repair is less likely to be feasible in these patients. There was no difference between small and medium-sized aneurysms and thus no anatomical reason for considering patients with small aneurysms for early endovascular repair.

Plasminogen activator inhibitor type 1 in breast cancer

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Background Plasminogen activator inhibitor (PAI) type 1 inhibits urokinase and tissue-type plasminogen activators (uPA and tPA) which play an important role in tumour metastasis. The aim of this study was to examine the role of PAI-1 in breast cancer using enzyme-linked immunosorbent assay (ELISA), Northern blotting and immunocytochemistry.

Results PAI-1 levels were measured by ELISA in 22 benign breast tumours, 194 primary breast cancers and in 31 breast cancer metastases. Levels of PAI-1 were significantly higher in malignant compared with benign breast tumours ($z = 2{\cdot}865$, $P = 0{\cdot}004$). Levels of PAI-1 were not significantly different when comparing primary and metastatic tumours. Levels of PAI-1 correlated significantly with uPA ($r = 0{\cdot}25$, $P = 0{\cdot}006$), tPA ($r = 0{\cdot}2$, $P = 0{\cdot}0062$) and PAI-2 ($r = 0{\cdot}175$, $P = 0{\cdot}0315$). PAI-1 had no correlation with tumour size, axillary nodal status or oestrogen receptor status. Using univariate and multivariate analysis, PAI-1 was a strong and independent prognostic marker for patient outcome (disease-free interval· relative risk (RR) 2·37, $\chi^2 = 13{\cdot}00$, $P = 0{\cdot}0003$; overall survival· RR 2·96, $\chi^2 = 16{\cdot}77$,

Spiral computed tomography *versus* aortography for measurement of aortic aneurysms undergoing endovascular repair

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Background Accurate measurement of aortoiliac length is essential for the safe construction and deployment of endovascular grafts. The purpose of this study was to evaluate the comparative utility of measurements obtained with spiral computed tomographic angiography (CTA) and those obtained by measuring aortography (MA) in patients undergoing endovascular aneurysm repair.

Methods The distance from the lowest renal artery and from the aortic bifurcation to the common iliac artery bifurcation was measured in 108 patients with abdominal aortic aneurysms using both CTA and MA Aortouniiliac endovascular grafts were constructed using these measurements and deployed in 73 patients Operative complications caused by graft–vessel length mismatch were recorded and the measurements used for graft construction reviewed to assess their utility.

Results The level of agreement between CTA and MA was high with 69 per cent of aortic and 75 per cent of iliac measurements within 1 cm and 92 per cent within 2 cm of each other. The mean(s.d) difference for renal artery to aortic bifurcation length was 0·35(1·2) cm and for common iliac artery length was 0·25(1·1) cm. MA renal artery to aortic bifurcation measurements were longer than those obtained by CTA, particularly in patients with large aneurysms (more than 6 5 cm) and lumen diameters greater than 5 cm ($\chi^2 = 29{\cdot}0$, 4 d.f, $P < 0{\cdot}0001$). Five patients developed intraoperative complications as a results of graft–vessel length mismatch. MA accuracy was implicated in three cases, human error in two and CTA in none.

Conclusion There is a high level of agreement between CTA and MA in the measurement of aortoiliac length MA overestimates renal artery to aortic bifurcation length in patients with large aneurysms and wide lumens. CTA is sufficiently accurate in the majority of cases to be used as the sole basis for the construction of endovascular grafts.

Outcome assessment in vascular surgery: a risk-adjusted analysis of morbidity and mortality

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Background When evaluating surgical performance, the use of crude mortality and morbidity data may be deceptive. The aim of this study was to use the Physiological and Operative Severity Score for enUmeration of Mortality and morbidity (POSSUM) system (a scoring system devised previously by others to predict mortality and morbidity rates) to produce a realistic measure of the performance of an academic vascular unit in terms of risk-adjusted mortality and morbidity.

Methods From January 1992 to December 1994, all patients admitted for surgery at the vascular service of the Johannesburg Hospital were scored using the POSSUM system. A quality measure was then derived by comparing the observed number of patients with an adverse postoperative outcome with the expected number of patients with such an outcome (O·E ratio). An O.E ratio of less than 1 indicates performance better than expected, whilst a ratio of greater than 1 worse than expected.

Results During the study period, 939 operative procedures were performed. The overall crude operative mortality rate was 14·2 per cent and the total complication rate 36·6 per cent. The predicted mortality and morbidity rates based on the POSSUM score were 17·5 and 45 per cent respectively This yielded an O:E ratio for mortality of 0·81 and for morbidity of 0·81.

Conclusion Crude mortality and morbidity rates can be misleading. A scoring system can produce an estimate of mortality and morbidity, thereby eliminating variations in surgical procedure and physiological status of the patient Despite the limitations of using a scoring system devised in another environment, the results of this study have brought about a modification in the authors' treatment protocols.

2,3 Butanedione monoxime protects isolated hearts from reperfusion injury after cardioplegic arrest

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Background Myocardial ischaemia and reperfusion, as regularly employed during cardiac surgery, may cause depressed cardiac function. A major determinant of this ischaemia and reperfusion injury is the marked increase of intracellular calcium, resulting in hypercontracture and tissue damage 2,3 Butanedione monoxime (BDM) reduces the calcium sensitivity of contractile proteins as well as transient calcium influx from the extracellular space and the sarcoplasmic reticulum. The aim of this study was to test the efficacy of initial BDM reperfusion in reducing reperfusion injury following cardioplegic arrest

Methods Some 40 guinea pig hearts were perfused in the Langendorff mode with modified Krebs' buffer (perfusion pressure 55 mmHg, 97 per cent oxygen, 3 per cent carbon dioxide 37°C). Left ventricular pressure was measured via a balloon inserted into the left ventricle. Coronary venous effluate was collected through a catheter in the pulmonary artery for determination of arterial partial pressure of oxygen and creatine kinase (CK). After stabilization and determination of baseline parameters, all hearts were arrested with St Thomas Hospital II cardioplegic solution and stored for 50 min at 37°C. On reperfusion, hearts were randomly assigned to one of four groups: immediate reperfusion with normal Krebs' control, initial reperfusion with BDM 20 $\text{mmol}\,l^{-1}$ in Krebs' for 5, 20 or 40 min before switching to normal Krebs' for 30 min (BDM-5, BDM-20 and BDM-40 respectively). Groups were compared by Students' *t* test, corrected by the Bonferroni-Holm procedure for multiple comparisons.

Results BDM depressed oxygen demand during initial reperfusion by about 50 per cent compared with baseline. The mean(s d.) increase of diastolic balloon pressure in control hearts to 30 ± 1 mmHg was ameliorated in BDM-20 and BDM-40 groups to 15(3) and 19(2) mmHg respectively. Recovery of left ventricular developed pressure reached only 47(3) per cent in control hearts, but was significantly improved to 66(5) per cent in the BDM-20 group only. Postischaemic release of CK was almost completely suppressed during initial BDM reperfusion in all treatment groups, however, 20 or 40 min of initial BDM perfusion were necessary to protect the hearts from CK release even after washout of the drug.

Conclusion It is concluded that initial BDM reperfusion effectively protects the heart from reperfusion damage following cardioplegic arrest. In this model, best protection was achieved with 20 min of BDM perfusion.

Intermediate-term results of endovascular aortic aneurysm repair

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The feasibility of endovascular exclusion of aortic aneurysms with encouraging early results has been reported by several groups. This study has been undertaken to evaluate the intermediate-term outcome of endovascular aortic aneurysm repair.

A total of 118 endovascular aneurysm repairs have been undertaken in this unit. Follow-up beyond 24 months is available through normal endothelium, and suggest that tumour cells can exploit PMN function to increase their metastatic ability

Antenatal glucocorticoid therapy suppresses angiotensin converting enzyme activity in rats with congenital diaphragmatic hernia

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Background Neonates with congenital diaphragmatic hernia (CDH) have a high morbidity and mortality rate due to pulmonary hypoplasia associated with pulmonary hypertension (PH). Antenatal glucocorticoid therapy improves surfactant biochemical immaturity, enhances lung compliance and induces morphological maturation in rats with CDH. Angiotensin converting enzyme (ACE) is implicated in the pathogenesis of PH. The aim of this study was to evaluate the effect of prenatal glucocorticoid therapy on ACE activity in the lungs of rats with CDH.

Methods CDH was induced in fetal rats by the maternal administration of 100 mg Nitrofen on day 9·5 of gestation (term = day 22) This study was approved by the UK home office, project licence number 40/1405. Dexamethasone (Dex) 0·25 mg kg^{-1} was given by intraperitoneal injection on days 18·5 and 19·5 before delivery of the fetuses by caesarean section on day 21·5. Control animals received olive oil (OO) by gavage and normal saline (NS) as vehicle injection. ACE activity was measured spectrophotometrically in the lungs of rats from four treatment groups: NS-CDH, NS-non-CDH, Dex-CDH and OO-NS

Results

	NS-CDH ($n=10$)	NS-non-CDH ($n=8$)	Dex-CDH ($n=11$)	OO-NS ($n=10$)
Total ACE activity (milliunits per lung)	10·7(1·3)*	16·2(1·6)†	9·6(1·0)‡	15·4(1·7)
Specific ACE activity (milliunits per mg protein)	6·3(1·1)	5·8(0·5)	4·0(0·4)§¶	4·4(0·4)

Values are mean(s.e.m.) *$P=0·002$; †$P=0·17$; ‡$P=0·004$ *versus* OO-NS controls; §$P=0·01$ *versus* NS-CDH and non-CDH; ¶$P=0·24$ *versus* OO-NS controls

Conclusion Antenatal steroids suppressed lung ACE *versus* activity in rats with CDH to levels seen in those of normal controls Prenatal glucocorticoids may therefore reduce the risk of PH developing in human newborns with antenatally diagnosed CDH.

Interleukin 10 reduces the systemic inflammatory response in a murine model of intestinal ischaemia–reperfusion

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Background The authors have shown previously that interleukin 10 (IL-10) decreases systemic levels of proinflammatory cytokines in several models of intra-abdominal sepsis Intestinal ischaemia–reperfusion (I/R) is known to increase systemic cytokine levels, as well as to activate neutrophils in distant organs. The effect of IL-10 on cytokine release and pulmonary neutrophil activity in a murine model of I/R has now been investigated.

Methods Forty female Swiss-Webster mice were divided into four groups Group 1 underwent 45 min of superior mesenteric artery (SMA) occlusion followed by 3 h of reperfusion (I/R) Group 2 underwent laparotomy alone (sham) Group 3 underwent I/R, but was treated with IL-10, 10 000 units intraperitoneally every 2 h, starting 1 h before reperfusion (pre-treatment). Group 4 was treated with an equal dose of IL-10, starting 1 h after reperfusion (post-treatment) Standard assays were performed for serum cytokine levels and lung myeloperoxidase activity (MPO).

Results

	Group 1	Group 2	Group 3	Group 4
TNF-α (pg ml^{-1})	291·6(56·5)	131·2(20·3)*	156·1(9·5)*	151·4(40·9)*
IL-6 (pg ml^{-1})	1521·4(312·7)	826·1(159·8)*	240·9(156·6)*	241·0(99·0)*
Lung MPO (units g^{-1})	4·01(0·14)	2·76(0·28)*	3·22(0·23)*	3·08(0·39)*

Values are mean(s.e.m.) TNF, tumour necrosis factor. *$P<0·05$ *versus* group 1

Conclusion IL-10 reduced the severity of systemic inflammation in a murine model of I/R. This effect was present whether IL-10 was given before or after reperfusion injury. These observations suggest that IL-10 may exert its effect by blocking both cytokine production and distant organ neutrophil activation.

Is neutrophil activation a physiological response of extreme exercise?

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Background It has been suggested that patients with intermittent claudication undergo repeated bouts of ischaemia–reperfusion injury during episodes of walking, and that this results in white cell activation, endothelial damage and enhanced atherogenesis This study aimed to determine if neutrophil activation or a change in total neutrophil count occurs in a healthy population exercised to exhaustion. These data were compared with that of patients with intermittent claudication exercised to their maximum walking distance.

Methods Some 20 claudicants (five women, 15 men) and 16 controls (six women, ten men) were enrolled. Neutrophil activation was determined by measurement of CD11b expression on flow cytometry. All participants had a resting determination of neutrophil count and CD11b expression before undertaking exercise using a standardized treadmill test. Claudicants were exercised to their maximum walking distance at 2·5 km h^{-1} and 10° incline. Controls were exercised to exhaustion at 5 km h^{-1} and 20° incline for a maximum of 20 min. Further determination of total neutrophil count and degree of neutrophil activation was undertaken at 1, 30 and 60 min after exercise.

Results Total neutrophil count increased significantly in both the control group and the claudicants following exercise (Wilcoxon signed rank test). There was no significant difference (Mann–Whitney *U* test) between the pre-exercise median CD11b fluorescence in the controls (2·54) of the claudicants (2·98). Following exhaustive exercise the median CD11b fluorescence in the control group (2·96) showed no significant increase compared with baseline Wilcoxon signed rank test. However, in the claudicants, median CD11b fluorescence increased significantly ($P<0·001$) to 4·59 compared with baseline Wilcoxon signed rank test and the control group Mann–Whitney *U* test

Conclusion Exhaustive exercise in healthy people without peripheral vascular disease results in an increase in total neutrophil count but without increase in neutrophil activation In contrast, patients with intermittent claudication demonstrate increased white cell activation with exercise. White cell activation is not a normal physiological response to exercise.

each time point) by measuring blood flow *in vivo*, arterial diameter and calculating wall shear stress (WSS) and comparing results with baseline control and the right iliac artery in each animal. Left and right iliac diameter, blood flow and WSS were the same at baseline. Left iliac diameter was no different from right iliac diameter at 1 h and 1 day, and left WSS increased more than threefold (43 *versus* 13 dyne cm^{-1}, $P<0{\cdot}01$) at 1 h. Left diameter increased at 3 days and reached a maximum (twice control diameter) at 90 days at which time WSS had returned to normal (12 dyne cm^{-2})).

	Control	1 h	3 days	14 days	21 days	42 days	90 days
Right							
Diameter	1·2	1·4	1·3	1 3	1·3	1·3	1·5
WSS	14·7	13·4	14·0	5·9	6·2	8·5	7·6
Left							
Diameter	1·1	1·3	1·4	1·6	1·8	1·9	2·3
WSS	16·8	43·1	37·5	30·0	35·7	20·0	11·7
Left/right diameter	1·0	1·0	1·1	1·3	1·4	1·4	1·6

The effect of NO inhibition on left iliac diameter was determined by adding L-NAME 0·5 mg/ml^{-1} (group I $n=6$) or L-NAME 2 mg/ml^{-1} (group II, $n=10$) to drinking water and comparing diameters with those in control rats (group III, $n=11$) 21 days after AVF construction. Rats treated with L-NAME had no significant increase in left diameter compared with right and had a smaller diameter than AVF control left iliac ($P<0{\cdot}01$) analysis of variance (ANOVA). The left/right diameter ratio was reduced in a dose-dependent manner (group I: mean(s.d.) 1·28(0·11) ($P=0{\cdot}07$), group II. 1·24(0·13) ($P=0{\cdot}01$); group III 1·43(0·23) ($P<0{\cdot}01$) ANOVA.

These findings show that NO inhibition by L-NAME reduces flow-induced arterial dilatation and suggest that NO is an important mediator of chronic flow-induced arterial remodelling

Genetic engineering of clonal hepatocytes to treat chronic liver failure

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Background Transplantation of hepatocytes has been shown to provide metabolic support during liver failure in experimental models. The potential clinical application of hepatocyte transplantation however, is limited by the need for readily available cells and a worldwide shortage of donor organs. A clonal hepatocyte cell line that could be grown economically *in vitro* would be an attractive solution to this problem.

Methods Primary Lewis rat hepatocytes were conditionally immortalized by retroviral transduction with a thermolabile mutant SV40 large T antigen and the arising clones characterized at the oncogen-permissive (33°C) and oncogen-restrictive (37–39°C) temperature. To evaluate the functional capacity, clonal hepatocytes were transplanted into a model of inducible hepatic encephalopathy (end-to-side portacaval shunt and administration of 3·4 mmol kg^{-1} ammonium acetate). Three groups of rats were examined: G1 ($n=7$) portacaval shunt; G2 ($n=7$) portacaval shunt and intrasplenic transplantation of 3×10^7 clonal hepatocytes 2 weeks after shunt surgery; and G3 ($n=7$) sham operation The hepatic encephalopathy was assessed by means of a coma scale consisting of assessment of various reflexes and by measuring the plasma ammonia level Three months after surgery, the spleens were removed for histological examination and *in situ* albumin messenger RNA hybridization.

Results The clonal hepatocytes proliferated in culture at 33°C and stopped growing at 37–39°C. When transplanted into the spleens of rats with a portacaval shunted, they protected recipients from hyperammonaemia-induced hepatic encephalopathy (mean(s.d.) plasma ammonia levels 30 min after intraperitoneal injection of ammonium acetate 4 weeks after hepatocyte transplantation: G1: 1250(370) mmol l^{-1}; G2: 632(246) mmol l^{-1}; G3: 381(179) mmol l^{-1} ($P<0{\cdot}05$)). Results of behavioural testing paralleled the plasma ammonia levels. In addition, the intrasplenically engrafted hepatocytes exhibited normal morphology, secreted bile and expressed albumin mRNA.

Conclusion These studies demonstrate that hepatocytes can be conditionally immortalized, expanded in culture and are capable of providing metabolic support in chronic liver insufficiency. Guards that make these oncogenially transformed cells clinically safe can be accomplished using currently available technologies.

Human neutrophils facilitate tumour cell migration: a novel mechanism for metastatic spread

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Background Tumour metastases remain a major cause of cancer-related deaths. To metastasize, tumour cells must shed into the blood stream (intravasation), survive in the circulation, and migrate through vascular walls and proliferate in the target organs (extravasation). It is suggested that tumour cell extravasation plays a key role in tumour metastasis. However, the precise mechanisms by which tumour cells migrate through normal endothelium remains unclear. Human neutrophils (PMNs) participate in the inflammatory response by transmigration through the endothelial barrier. However, it is unknown whether this facility of transmigration of PMNs can be employed by tumour cells to assist the metastatic process. This study was designed to test the hypothesis that normal human PMN function is altered by tumour cells and that these PMNs can assist tumour cell migration through normal endothelial monolayers.

Methods Human PMNs isolated from healthy donors by density gradient were incubated with the breast metastatic cell line, MDA-MB-231, cell-conditioned medium (TCM). Human umbilical vein endothelial cells (HUVECs) isolated from umbilical veins were plated in a collagen-coated Transwell and cultured at 37°C, 5 per cent carbon dioxide for 30 h to form confluent monolayers. TCM-treated PMNs and MDA cells were co-cultured at a 2:1 ratio for 1 h and then plated on HUVEC monolayers to assess tumour cell migration. PMN respiratory burst, phagocytosis, and CD11a, CD11b, CD18, and intercellular cell adhesion molecule (ICAM) 1 expression were assessed by flow cytometry. Migrated tumour cells and PMNs were distinguished by flow cytometry and morphology, and counted at different time points.

Results TCM-treated PMNs induced tumour cell migration through normal human vascular endothelium. PMNs treated with TCM resulted in significant decreases in PMN respiratory burst and phagocytosis ($P<0{\cdot}05$ *versus* normal medium). Moreover, TCM markedly enhanced PMN adhesion receptor expression including CD11b and CD18 ($P<0{\cdot}05$ *versus* normal medium) MDA-MB-231 cells themselves did not migrate spontaneously through the HUVEC monolayers. FACS analysis revealed that these tumour cells expressed (ICAM) 1 but did not express CD11a, CD11b, and CD18.

Conclusion These results indicate that TCM-treated human PMNs may serve as a carrier to assist tumour cell migration

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Surgical Research Society Abstracts

The following abstracts were presented at the 86th meeting of the Surgical Research Society. The meeting was organized by the Department of Surgery, University of Nottingham, and held on 9-11 July 1997 in the University of Nottingham. One hundred and fifty-nine papers were presented during the scientific sessions. The Patey Prize was awarded to Mr P. J. Drew for his paper entitled 'Clinical application of dynamic magnetic resonance mammography – evaluation of 622 scans'.

Endoleaks, thrombus distribution and changes in aneurysm size following endovascular repair

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Background Persistent pulsatile blood flow around the stent graft after endovascular repair ('endoleak') has been documented as a cause of complications and graft failure. However, few data exist on the problems of ongoing perfusion of the aneurysm sac from the lumbar arteries. The aims of this study were to determine (1) the fate of the aneurysm sac after endovascular repair, (2) the significance of collateral lumbar artery blood flow and (3) the relationship between thrombus distribution within the aneurysm sac and the development of a 'lumbar endoleak'.

Methods Some 68 patients treated with endovascular stent grafts were followed up with spiral computed tomography for a median of 11 (range 3–27) months. The cross-sectional area of the aneurysm was measured at the point of maximum diameter before and after operation. The distribution and quantity of thrombus was recorded before operation and this was related to changes in aneurysm size and the development of lumbar endoleaks after operation.

Results Postoperative aneurysm size changes were as follows

Postop. size change	Endoleak	No endoleak	Total
Increase >1 cm^2	10	12	22
No change	4	10	14
Decrease >1 cm^2	0	32	32
Total	14	54	68

Difference between endoleak and no endoleak groups: $\chi^2 = 17{\cdot}1$, 2 d.f., $P < 0{\cdot}001$).

Nine endoleaks were from patient lumbar arteries. The presence of thick circumferential or posteriorly placed thrombus protected against endoleak from lumbar vessels (none of 21 cases) compared with no or anteriorly placed thrombus (nine of 47 cases)) χ^2 with Yates' correction $= 3{\cdot}11$, 1 d.f., $P < 0{\cdot}1$)

Conclusion Lumbar endoleak consistently results in aneurysm expansion or at least no decrease in size. A significant number of aneurysms increase in size despite no evidence of an endoleak. Patterns of thrombus distribution may be able to predict patients at risk from persistent endoleak via lumbar vessels.

Transhiatal oesophageal resection *versus* transthoracic oesophageal resection with two-fields lymphadenectomy: interim results of a randomized study

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Long-term prognosis after potentially curative resection for oesophageal cancer is still poor. Non-randomized studies suggest that extensive lymphadenectomy in addition to wide local excision of the primary tumour provides a beneficial effect on 5-year survival, but the procedure is possibly associated with a high risk of postoperative complications.

A randomized multicentre trial has been initiated comparing two different surgical treatments for patients with a potentially curable adenocarcinoma of the oesophagus and/or gastro-oesophageal junction, i.e. transhiatal oesophagectomy without thoracotomy (THE) *versus* transthoracic oesophagectomy with two-fields lymph node dissection (TTE). The aim of this interim analysis was (1) to evaluate the occurrence of postoperative complications in both groups and (2) to assess quality control on the extended lymph node dissection. Between April 1994 and November 1996, 80 patients were randomized. Data analysis was based on the intention-to-treat principle The two groups were comparable regarding age, sex, American Society of Anesthesiologists classification, tumour localization and pathological stage.

	THE	TTE	*P**
No of patients	38	42	
Median (range) ICU stay (days)	2 (0–21)	6 (0–35)	0·0005
Median (range) hospital stay (days)	15 (8–53)	22 (7–117)	0·0002
In-hospital deaths*	0 (0)	3 (7)	n.s.
Pulmonary complications*	8 (21)	26 (62)	0·0002
Chylothorax*	1 (3)	5 (12)	n.s.
Clinical leakage*	3 (8)	2 (5)	n.s.
Median (range) no. of lymph nodes resected	15 (4–40)	28 (5–56)	0·0001

*Values in parentheses are percentages. ICU, intensive care unit; n.s., not significant †Mann–Whitney *U* test. χ^2 or Fisher's exact test when appropriate

Transthoracic oesophageal resection is associated with increased postoperative morbidity, compared with the transhiatal resection. Furthermore, this interim analysis indicates that an adequate extended lymph node dissection has been achieved. It is concluded that continuation of this trial with careful monitoring is justified to establish whether the extended thoracic resection sufficiently improves long-term survival to compensate for the increase in postoperative morbidity.

Flow-induced arterial remodelling is inhibited by suppression of nitric oxide

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Acute arterial dilatation in response to increased blood flow depends on endothelial production of nitric oxide (NO). However, the role of NO in chronic flow-induced arterial remodelling is unknown. Blood flow was increased in the left iliac artery in 49 male 300–400 Sprague–Dawley rats by constructing a left femoral arteriovenous fistula (AVF). The time course of adaptive changes after AVF construction was determined at 1 h, and 1, 3, 7, 14, 21, 42 and 90 days ($n = 4$–9 at

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Table 4 Surgical complications and hospital deaths according to surgical procedure

		Combined resection		Surgical complications			
	n	Splenectomy	Pancreatectomy	Leakage	Abscess*	Fistula	Hospital deaths
Distal gastrectomy							
D_1	258	No	No	5	15	1	9
D_2	199	No	No	14	18	2	11
D_1	7	Yes	No	1	0	0	0
D_2	6	Yes	No	2	1	1	3
Total gastrectomy							
D_1	81	No	No	7	6	1	4
D_2	7	No	No	0	0	0	2
D_1	24	Yes	No	0	2	0	0
D_2	21	Yes	No	5	5	0	5
D_1	10	Yes	Yes	3	5	1	2
D_2	97	Yes	Yes	8	25	7	11

*Intra-abdominal, †pancreatic

between D_1 and D_2 after a distal gastrectomy is no longer statistically significant (3·5 *versus* 5·5 per cent). Another explanation for the effect of splenectomy might be its immunosuppressive effect[20], further evaluation of which is necessary.

Distal pancreatectomy is often associated with intra-abdominal abscess formation[21], as this trial confirmed. In multivariate analyses for surgical complications it was the most significant factor (RR 3·34). The value of pancreas-preserving total gastrectomy has been assessed in Japanese patients[22] but not, as yet, in Western patients.

The increased risk of hospital death and morbidity after combined resection of these organs in this study suggests that the benefit of combined resection is limited in Western patients, as reported by Brady and colleagues[23]. The decision to resect the spleen, or spleen and pancreas, in Western patients requires careful estimation of risks and benefits in each case.

The type of gastrectomy seemed a less important factor in this study than in the series of Viste *et al.*[19], but was still a significant factor for surgical complications.

Although the extent of nodal dissection (D_1 *versus* D_2) showed no significance for surgical complications, significantly more anastomotic leaks were observed after D_2 distal gastrectomy even after exclusion of the cases associated with splenectomy. This is probably due to ischaemia of the remnant stomach, possibly from division of some of the short gastric vessels. It may also occur when linear staplers are used for side-to-side gastrojejunostomy, as this divides the intramural vascular network of the gastric stump, causing ischaemia of the part between the anastomosis and the division line of the stomach. The safety of this technique after D_2 gastrectomy should be investigated.

The high incidence of infective complications after a total gastrectomy with pancreaticosplenectomy highlights the issue of the routine use of prophylactic drains. Japanese surgeons believe that proper placement and retention of drainage tubes in the left subphrenic space is essential after D_2 total gastrectomy with pancreaticosplenectomy. This practice was not followed during most of the Dutch trial, but there are insufficient data to determine whether this contributed to the much higher mortality rate in Dutch patients which occurred with the same incidence of morbidity as in Japanese patients[1,12].

Different aspects of 'experience' were studied (*Table 2*), but neither univariate nor multivariate analysis showed any statistically significant association. Only 12·0 per cent of the 711 curable patients were treated after an experience of 15 cases in each hospital in the 4 years of the trial. However, the possibility cannot be excluded that the apparent absence of a learning curve reflected inadequate experience during the whole trial period, as some correspondents have suggested[14]. The issue of whether gastric cancer surgery should remain within the territory of general surgeons has been discussed recently[24,25]. The hospital mortality and morbidity rates associated with gastric cancer surgery are almost the same as or even higher than those associated with pancreaticoduodenectomy[26], major liver resection[27] and oesophagectomy[28,29]. In view of the much lower mortality rate reported by specialized centres[15–17], it is concluded that treatment of gastric cancer should be the territory of a multidisciplinary team of committed specialists in all areas to provide optimal results. Preoperative assessment of the lesion and the patient, and perioperative management, are as important as the operation itself.

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3·79), while pancreatectomy showed the largest relative risk (5·04) for surgical complications. Resection line involvement by cancer did not affect significantly the risk of hospital death or surgical complications. The factors which showed the largest relative risk for overall complications were pancreatectomy (RR 3·03 (95 per cent confidence interval (c.i.) 1·98–4·65)), splenectomy (RR 2·69 (95 per cent c.i. 1·87–3·87)), nodal dissection (RR 2·29 (95 per cent c.i. 1·65–3·17)) and type of gastrectomy (RR 2·00 (95 per cent c.i. 1·43–2·78)). Sex and age showed a significant but much smaller relative risk (1·49 and 1·66 respectively) for overall complications than for mortality.

Factors related to experience had no significant impact on morbidity or hospital mortality rates, although the mortality rate in the hands of the Japanese surgeon (3·0 per cent) was much smaller than that of others (10·4 per cent) within the D_2 group. Surgical complication rates after D_2 resection by the Japanese surgeon and the others were almost the same, 21·2 and 21·8 per cent respectively.

Multivariate analysis

The results of multivariate analyses for hospital mortality, overall and surgical complications are shown in *Table 3*. Age and sex affected hospital death but had less impact on morbidity. Splenectomy showed the largest relative risk for overall complications. Distal pancreatectomy showed by far the largest relative risk for surgical complications, followed by the type of gastrectomy, although it disappeared in the stepwise logistic regression analysis as a risk factor for death and overall complications because of its strong correlation with splenectomy. Similarly, splenectomy disappeared in the analysis of surgical complications.

Table 3 Risk factors for hospital death, and overall and surgical complications selected in multivariate analysis

	n	No. of patients affected*	Relative risk†
Hospital death	711	47 (6·6)	
Node dissection			
D_1	380	15 (3·9)	
D_2	331	32 (9·7)	2·13 (1·05–4·32)
Splenectomy			
No	546	26 (4·8)	
Yes	165	21 (12·7)	2·16 (1·09–4·28)
Sex			
F	308	12 (3·9)	
M	403	35 (8·7)	2·51 (1·24–5·08)
Age (years)			
≤65	346	10 (2·9)	
>65	365	37 (10·1)	4·35 (2·07–9·15)
Overall complications	711	236 (33·2)	
Node dissection			
D_1	380	94 (24·7)	
D_2	331	142 (42·9)	1·96 (1·38–2·78)
Splenectomy			
No	546	152 (27·8)	
Yes	165	84 (50·9)	2·13 (1·44–3·16)
Sex			
F	308	87 (28·2)	
M	403	149 (37·0)	1·56 (1·11–2·19)
Age (years)			
≤65	346	95 (27·5)	
>65	365	141 (38·6)	1·86 (1·32–2·61)
Surgical complications			
Total	711	113 (15·9)	
Pancreatectomy			
No	603	70 (11·6)	
Yes	108	43 (39·8)	3·34 (1·81–6·14)
Gastrectomy			
Distal	470	48 (10·2)	
Total	241	65 (27·0)	1·74 (1·00–3·04)

Values in parentheses are *percentages and †95 per cent confidence intervals

Since pancreatectomy and splenectomy were strong risk factors, especially for surgical complications (see *Tables 2* and *3*), the three components of the surgical complications were tabulated according to type of gastrectomy, extent of nodal dissection, and concomitant splenectomy and/or pancreatectomy (*Table 4*). Significantly more patients in the D_2 group (126 of 331, 38·1 per cent) than in the D_1 group (115 of 380, 30·3 per cent) underwent a total gastrectomy ($P<0{\cdot}05$). Some 24 of 115 patients in the D_1 group who underwent a total gastrectomy also had splenectomy (without pancreatectomy) in spite of the protocol, even though they did not have a T_4 tumour invading either the pancreas or the spleen.

A distal pancreatectomy was carried out in ten patients in the D_1 group to remove tumours directly invading the pancreas. For distal gastrectomy without splenectomy, the difference in mortality rate between the D_1 and D_2 groups was much smaller than in the whole population. Considerably more anastomotic leaks were observed after distal gastrectomy in the D_2 group than in the D_1 group.

Discussion

This study was carried out in more than 80 hospitals with special attention to quality control of surgery. The only criterion of eligibility was that patients had to be fit for both operations (D_1 or D_2)[11]. The age limit was 85 years. Therefore, this study was carried out using almost entirely unselected patients. The results permit an interesting analysis of the operative mortality and morbidity rates of gastric cancer surgery since the subgroups are large, the treatment allocation was random and the care given was representative of practice in the Netherlands.

The odds ratio for age and sex were much smaller for complications than for hospital death, as reported by Viste *et al.*[19]. This means that these two factors correlate better with the ability to tolerate complications than with their occurrence.

Splenectomy was the factor which most affected morbidity, while it showed the third largest relative risk for hospital death. It always showed a larger relative risk than nodal dissection (D_1 or D_2).

The adverse effect of splenectomy may be explained by the fact that it causes significant ischaemia of the remnant stomach when performed in association with a D_2 distal gastrectomy, in which the left gastric artery is divided at its origin and the short gastric arteries are the only blood supply to the stump. This is not such a problem in D_1 distal gastrectomy where the left gastric artery is divided more peripherally. If splenectomy is unavoidable because of injury during D_2 gastrectomy, total gastrectomy should be carried out regardless of the location of the primary tumour. Three of six patients who underwent splenectomy with D_2 distal gastrectomy died after operation, while none of the seven with splenectomy and D_1 distal gastrectomy died. D_2 distal gastrectomy with splenectomy amounts to a fundamental technical error. If these patients are excluded, the difference in mortality rate abdominal abscess and pancreatic fistula were defined as surgical complications.

Factors which might affect hospital deaths, overall complications, and surgical complications were evaluated by univariate analysis using cross-tabulations. The χ^2 test was used to assess differences in proportions. The independent contribution of various factors was assessed by multivariate analysis using stepwise logistic regression analysis. Factors analysed were node dissection, splenectomy, pancreatectomy, resection line involvement by cancer, type of gastrectomy, sex, age, and three factors regarding experience, i.e. teaching *versus* non-teaching hospitals, the first 15 patients enrolled in the trial in the hospital *versus* those enrolled subsequently, and first and second halves of the trial.

Table 1 Type of gastrectomy and combined spleen and/or pancreas resection in 711 patients

		No pancreatectomy		With pancreatectomy	
	n	No splenectomy	With splenectomy	No splenectomy	With splenectomy
D_1 ($n = 380$)					
Distal gastrectomy	265	258	7	0	0
Total gastrectomy	115	81	24	0	10
D_2 ($n = 331$)					
Distal gastrectomy	205	199	6	0	0
Total gastrectomy	126	7	21	1	97
Total	711	545	58	1	107

Results

After 711 curative operations, 47 hospital deaths (6·6 per cent), 236 overall complications (33·2 per cent), and 113 surgical complications (15·9 per cent) were registered. The type of gastrectomy and combined spleen and/or pancreas resection carried out is shown in *Table 1*. In total, 470 patients underwent distal gastrectomy and 241 total gastrectomy. Splenectomy was carried out in 165 patients (23·2 per cent), associated with total gastrectomy in 152 and with partial gastrectomy in 13.

Univariate analysis

Univariate analyses of risk factors for hospital deaths and for surgical complications are shown in *Table 2*. For hospital deaths, age showed the greatest relative risk (RR

Table 2 Univariate analysis of risk factors for death and surgical complications

		Hospital death		Surgical complications	
	n	Incidence*	Relative risk†	Incidence*	Relative risk†
Total	711	47 (6·6)		113 (15·9)	
Surgery related					
Node dissection					
D_1	380	15 (3·9)		41 (10·8)	
D_2	331	32 (9·7)	2·60 (1·37–4·96)	72 (21·8)	2·30 (1·50–3·51)
Splenectomy					
No	546	26 (4·8)		59 (10·8)	
Yes	165	21 (12·7)	2·92 (1·57–5·40)	54 (32·7)	4·02 (2·61–6·18)
Pancreatectomy					
No	603	34 (5·6)		70 (11·6)	
Yes	108	13 (12·0)	2·29 (1·15–4·56)	43 (39·8)	5·04 (3·15–8·04)
Resection line					
Clear	670	45 (6·7)		103 (15·4)	
Involved with cancer	41	2 (5)	0·71 (0·16–3·14)	10 (24)	1·78 (0·83–3·79)
Gastrectomy					
Distal	470	23 (4·9)		48 (10·2)	
Total	241	24 (10·0)	2·15 (1·17–3·94)	65 (27·0)	3·25 (2·13–4·95)
Demography					
Sex					
F	308	12 (3·9)		43 (14·0)	
M	403	35 (8·7)	2·35 (1·18–4·66)	70 (17·4)	1·30 (0·85–1·97)
Age (years)					
≤65	346	10 (2·9)		48 (13·9)	
>65	365	37 (10·1)	3·79 (1·83–7·86)	65 (17·8)	1·35 (0·89–2·04)
Experience					
Year of surgery					
After 1991	270	15 (5·6)		39 (14·4)	
1991 or before	441	32 (7·3)	1·33 (0·70–2·54)	74 (16·8)	1·20 (0·78–1·84)
Teaching hospital					
No	341	16 (4·7)		45 (13·2)	
Yes	370	31 (8·4)	1·86 (0·98–3·51)	68 (18·4)	1·48 (0·98–2·25)
Experience					
>15th patient	85	7 (8)		11 (13)	
≤15th patient	626	40 (6·4)	0·76 (0·32–1·79)	102 (16·3)	1·30 (0·66–2·59)

Values in parentheses are *percentages and †95 per cent confidence intervals

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Risk factors for surgical treatment in the Dutch gastric cancer trial

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Background A multicentre randomized study of surgical treatment of gastric cancer has shown increased mortality and morbidity rates in patients having D_2 resection. The aim of this report is to analyse risk factors in these patients.

Methods In a prospective randomized trial, comparing two types of lymphadenectomy for curable gastric cancer, risk factors for hospital death and morbidity in 711 patients treated with curative intent were evaluated by multivariate analysis using stepwise regression analysis.

Results Age greater than 65 years and male sex were the most important risk factors for death (relative risk (RR) 4·35 (95 per cent confidence interval (c.i.) 2·07–9·15) and 2·51 (95 per cent c.i. 1·24–5·08) respectively). The extent of nodal dissection was also a significant risk factor for death (RR 2·13). For overall complications, splenectomy was the most important risk factor (RR 2·13 (95 per cent c.i. 1·44–3·16)), while pancreatectomy and type of gastrectomy were the only factors significantly influencing the occurrence of major surgical complications.

Conclusion The cumulative mortality risks of these factors should be considered carefully when planning surgery for individual patients.

In Japan, extended lymph node dissection is now part of standard treatment for advanced gastric cancer[1]. In some Western countries the same approach is taken, particularly in specialized centres for gastrointestinal malignancy[2–4], but there is widespread scepticism, shown by the low percentage of systematic radical nodal dissections performed (27 per cent in Europe[5] and 4·7 per cent in the USA[6]). A major reason for this scepticism is fear of increased morbidity and mortality rates[7–10]. The hospital mortality and morbidity rates of patients treated in the Dutch Gastric Cancer Trial (DGCT), comparing the D_1 (dissection of perigastric nodes only) and D_2 (extended nodal dissection including regional lymph nodes) operations have been reported previously[11,12]. A statistically significant difference in hospital mortality and morbidity rates between D_1 and D_2 dissections was observed in this multicentre trial. It was concluded that D_2 dissection applied in general hospitals by general surgeons carried a much greater risk than D_1 dissection, despite great efforts to control the quality of surgery[11–13].

Critics of this paper[12] pointed out incorrect indications for pancreaticosplenectomy and insufficient experience in each hospital[14]. Several specialist centres in Europe have reported excellent results from extended surgery[15–17], although not in randomized controlled trials. By the nature of a randomized control trial, all eligible patients in the Dutch series were treated in a uniform way (either D_1 or D_2 dissection) irrespective of age and physical condition. This minimum bias from patient selection permitted a precise analysis of risk factors for morbidity and hospital mortality rates after gastric cancer surgery. The aim of this paper is to evaluate the importance of each risk factor affecting morbidity and mortality rates, including the extent of nodal dissection and combined resection of the spleen and the pancreas.

Patients and methods

Patients

Some 1078 patients were registered and randomized in the trial between August 1989 and July 1993. Of these, 711 eligible patients who underwent curative surgery were included in this study. Eligibility criteria and method of randomization were as reported previously[11–13].

Surgical treatment

The manual of the Japanese Society for Gastric Cancer[18] was used to define the surgical treatment (D_1 and D_2) and pathological assessment (T and N). Quality control of surgery was as reported previously[11–13].

A macroscopically completely removable tumour, without peritoneal or liver metastasis, and without lymph node metastasis beyond N_2, was regarded as curable. Patients with such tumours underwent the allocated surgery, although some proved subsequently to be incurable on histological examination of the resection lines. The extent of gastric resection, i.e. total or distal, was always decided by the location of the primary tumour[11]. Splenectomy was always required when a total gastrectomy was indicated in the D_2 procedure A distal pancreatectomy was associated with total gastrectomy only if the serosa was invaded by cancer or if the tumour was located on the greater curvature or on the posterior wall of the gastric body. In the D_1 dissection, the spleen and the tail of the pancreas were preserved unless directly invaded by tumour. The alimentary tract was reconstructed according to the preferred method of the surgeon Drainage tubes were inserted routinely after D_2 gastrectomy for the initial 4 months of the trial, but not routinely thereafter.

Assessment of risk factors

The postoperative course was assessed from the trial forms. The hospital mortality rate included all deaths in hospital after operation and deaths within 30 days of operation. Leakage, intra-

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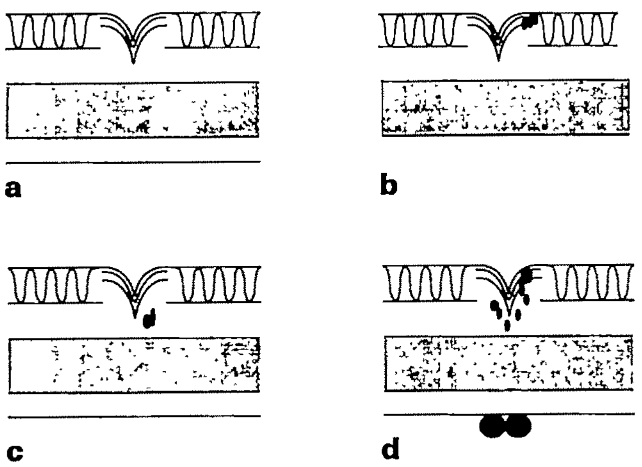

Fig. 1 Presence of cancer cells on the cut surface of the gastrectomy specimen. a No cancer cells remained in the specimen (patients 1–4); b cancer cells remained in the mucosa around the resection margin (patients 5–9); c cancer cells infiltrated into the submucosa (patient 10); and d there was evidence of a coexisting depressed lesion adjacent to the scar, in which cancer cells had invaded the deeper layer of the submucosa and metastasized to regional lymph nodes (patient 11)

Table 4 Comparison of the depth of invasion between endoscopically- and surgically-resected specimens

Depth of invasion in endoscopically-resected specimen	No. of cases	Depth of invasion in surgically-resected specimen		
		None*	Mucosa	Submucosa
Mucosa	5	1	4	0
Submucosa	6	3	1	2

*No cancer cells remaining in the specimen

case the metastases could have resulted from an advanced colon cancer treated 9 years previously.

Discussion

The proportion of patients who required additional gastric surgery after EMR diminished during the study. In earlier years, EMR remained a challenge. From this retrospective analysis, it was found that two patients were not ideal candidates for EMR. Improvements in recent years may be due to use of ultrasonic endoscopy before EMR to assess the depth of invasion and the application of electrocautery to kill cancer cells around the resected margin.

Cure is a mandatory goal for the treatment of early gastric cancer. Understanding the indications and limitations of EMR is necessary. Although the size and histology affected the cure rate with EMR[1], the location of the lesion seems to be another important factor. In the present study, incomplete excision usually occurred when lesions had a diameter exceeding 15 mm and were situated in the body or the cardia. Takekoshi *et al.*[1] reported an incomplete resection rate of 4 per cent for lesions of the antrum, but 10–20 per cent for lesions of the gastric angle or body. The entire margin is difficult to visualize using front-view endoscopy, especially in lesions on the anterior or posterior wall of the gastric angle or body. To increase the efficacy of EMR, smaller lesions should be resected, especially if located in the body or cardia. Accurate diagnosis of the width and depth of invasion is indispensable before EMR. In this series, one raised lesion with a diameter of 2 cm had been incompletely resected by EMR, but a coexisting depressed lesion adjacent to the scar was subsequently found on histological examination. The surrounding mucosa adjacent to an early cancer should be biopsied so as not to overlook coexisting lesions.

Assessment of the depth of invasion from an endoscopically-resected specimen is important for making therapeutic decisions. Overestimation may result in inappropriate gastrectomy. Underestimation may lead to failure of treatment. In the present study, assessment of the depth of entire invasion from the endoscopically-resected specimen was correct in six of 11 patients. In the remaining five patients, the depth of invasion was overestimated. These findings suggest that depth of invasion observed in the endoscopically-resected specimen may represent the depth of the entire lesion. There is general agreement that the incidence of lymph node metastasis is increased in submucosal carcinoma up to a rate of 20 per cent compared with 3 per cent in mucosal carcinoma[4,5]. If cancer cells are found in lymphatic vessels or invading the deeper layer of the submucosa, surgical excision is the treatment of choice. The optimum treatment when the invasion is limited to the superficial layer of submucosa but lymphatic vessels are not infiltrated is unknown. Takekoshi *et al.*[1] recommended careful follow-up without surgical intervention for such patients. However, a small number of patients have lymph node metastases, even in association with lesions limited to the mucosa[4,5], or invading the superficial submucosal layer[6]. Ohta *et al.*[4] reported a case of flat type mucosal cancer (type IIb) measuring 5 mm in diameter with lymph node metastasis. There may be a highly malignant type of early gastric cancer even at an extremely early stage without submucosal invasion.

The authors' present policy is to perform gastrectomy when malignant cells are present in the submucosal layer in the endoscopically-resected specimen. When malignant cells extend to the mucosa around the resection margin, non-invasive treatments such as repeated EMR, laser coagulation[7] or limited surgery are preferable.

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intestinal lumen and had TCD alone. The authors concluded that combination procedures were not necessary.

There have been two cautionary reports of possible stent-induced stricture. Barthet and colleagues[12] noted one patient who, after transpapillary stenting, developed scarring at the site of the connection of the pseudocyst to the main pancreatic duct. The stent had been within the pseudocyst cavity itself and may have been responsible for this narrowing. It was not possible to traverse the stricture for dilatation but the patient remained asymptomatic at 1 year. Kozarek *et al.*[18] noted a single patient who appeared to have a fixed ductal stenosis after stenting of the duct of Santorini with a 5-Fr stent which blocked causing infection and was replaced with a 7-Fr stent. They also reported minor ductal changes in eight of 16 patients who had repeat ERCP at various times after stent removal. None appeared to have any functional changes. It is not clear whether these changes were stent induced, related to infection in the presence of a stent, progression of the disease process or, in the case of side branch changes, due to differences with contrast injection volumes and pressures. In a series of 32 patients with chronic pancreatitis undergoing long-term duct stenting for various indications there have been no clinical problems at 3 years[31].

Transmural pseudocyst drainage

A number of essential prerequisites are necessary before transmural drainage is undertaken. The pseudocyst must be in the pancreatic head or body, which occurs in 70 per cent of cases[9]. The distance between the pseudocyst and the gastric and duodenal wall must be less than 1 cm measured on computed tomography or endoscopic ultrasonography (*Fig. 1*) and there must be a clear impression of the pseudocyst into the wall of the stomach or duodenum at endoscopy (*Fig. 2*)[11,19,20,24,32]. These criteria are met in 55 per cent of pseudocysts complicating chronic pancreatitis and 27 per cent complicating acute pancreatitis[33].

The technique of transmural drainage is similar for both ECD and ECG. A side-viewing endoscope is used to identify the area of maximal bulge and a needle knife papillotome is used to make a diathermy incision to enter the pseudocyst. Confirmation of pseudocyst entry is immediate as there is rapid fluid loss through the entry site. It is important to maintain access at this stage as it can be difficult to identify the site of entry after partial collapse of the pseudocyst[34]. This can be achieved by preloading the needle knife through a 10-Fr coaxial sheath so that after puncture the coaxial sheath can be advanced immediately. A number of devices have been designed to make access easier. Cremer *et al.*[34] developed a 10-Fr coaxial sheath with a circular cautery tip. Once access is established with the needle knife the coaxial sheath is advanced into the pseudocyst enlarging the opening to approximately 3 mm. Knecht and Kozarek[35] described a modified standard 7-Fr sphincterotome which has had the tip cut back to allow 4 mm of the diathermy wire to protrude. There is thus a second channel through which a 0·9-mm (0·035 inch) guidewire can be inserted immediately the pseudocyst is punctured to maintain access.

The size of the cystgastrostomy has varied from 3 to 50 mm[11,21]. A standard sphincterome is used to increase the size of the opening into the pseudocyst. A 7–10-Fr stent may be left within the cyst cavity to maintain patency; the stent may be of the straight Amsterdam type[11,22], pigtail, single or double[12,20,21]. The stent is left in place for 2–4 months or until ultrasonographic confirmation of cyst resolution. Some authors routinely insert a nasocystic catheter; others use this only when the pseudocyst fluid is turbid or contains pus[11,24], allowing washout with saline[11] or antibiotic and saline[24] for 2–7 days after which it is replaced by a standard stent.

In addition to the patients included in *Tables 1–3* there have been a number of series in which TCD and transmural drainage procedures have been performed in the same patient[11–13,20] or in which distinction between ECD and ECG has not been made[13]. The results of these studies are shown in *Table 4*.

Endoscopic cystogastrostomy

In the combined series of 50 patients (*Table 1*), pseudocyst drainage was achieved in 82 per cent with a recurrence rate of 18 per cent with a median follow-up of 9–48 months. Three of the recurrences were successfully treated by repeat endoscopic drainage and the remainder were dealt with surgically. There were no deaths and the major complications were bleeding (8 per cent) and perforation (8 per cent).

Bleeding is the most serious complication of ECG and is often due to opening into a large vessel[36] requiring surgical intervention. In addition to the four cases in *Table*

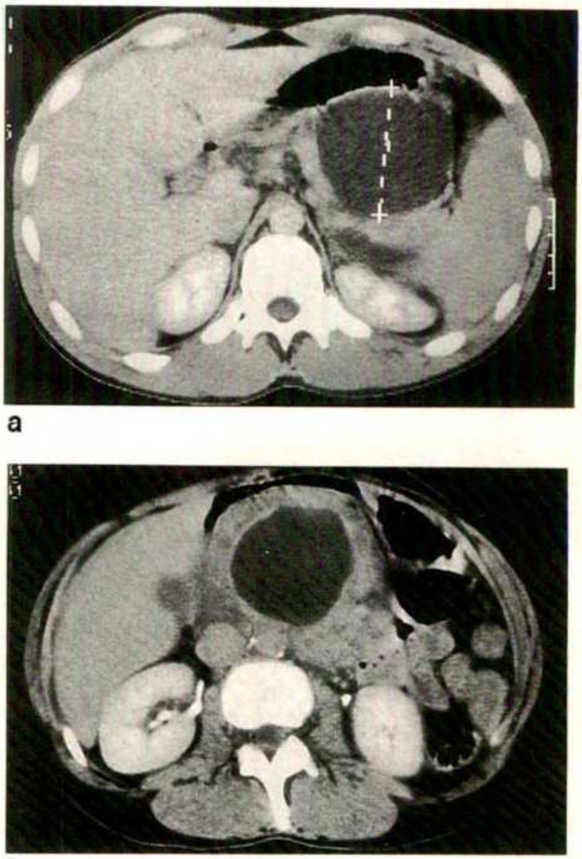

Fig. 1 **a** Thin walled pseudocyst suitable for endoscopic drainage and **b** thick walled pseudocyst unsuitable for endoscopic drainage

1, there were two further cases of bleeding associated with ECG performed in association with TCD (*Table 4*). Successful local treatment by cautery and local injection sclerotherapy was possible in only one of these six cases[11]. The collective incidence of bleeding requiring surgical intervention taken from studies included in *Tables 1* and *4* is 7 per cent (five of 76 patients). Bleeding is usually caused during the enlargement of the cystogastrostomy puncture with the sphincterome. The technique and size of the gastrostomy used in the various studies has varied from just large enough to allow insertion of a stent to a larger surgical sized gastrostomy extended with a sphincterotomy knife up to 20–50 mm[21–37]. Use of a small incision has been advocated to reduce complications from bleeding[11,24]. An alternative to sphincterotomy may be balloon dilatation to enlarge the fistula[38,39]. Proponents of larger gastrostomies hope to achieve better drainage, particularly of infected pseudocysts or those containing necrotic debris, but there is no clear correlation between ECG size and recurrence rate (*Table 1*).

Endoscopic cystoduodenostomy

In a total of 71 patients successful drainage was achieved in 89 per cent with a recurrence rate of only 6 per cent with a median follow-up of 9–48 months. These results are better than those of ECG which may be related to the observation that ECDs remain patent longer than ECGs[19,22]. Cremer *et al.*[19] had cause to repeat ERCP on nine patients with ECD and found six patent at 4 months whereas none of the patients with ECG had patent connections at the same time point. Inadequate drainage and early recurrence has been noted with open cystogastrostomy[1]. The cystoduodenal fistula remains patent while pancreatic secretions persist and in most cases only closes when the pseudocyst has resolved[19].

Complications were less common with ECD. Perforation occurred in three patients (4 per cent) and was successfully treated conservatively with antibiotics. Perforation is usually contained with ECD because leakage is invariably retroperitoneal, whereas perforation with ECG tends to be intraperitoneal. Severe bleeding occurred in three patients (4 per cent) and in one further patient in the combined series (*Table 4*). Surgery was required in three of four patients giving an overall incidence of bleeding requiring surgery of 3 per cent (three of 90 patients). Two patients with bleeding were reported by Sahel and colleagues[24], one of whom died. In both instances the bleeding originated from within the cyst secondary to a pseudoaneurysm. A variceal injection needle can be used to aspirate the pseudocyst before cutting into it and aspiration of blood-stained fluid may be regarded as an indication for open surgical drainage to permit control of vessels before decompression[37].

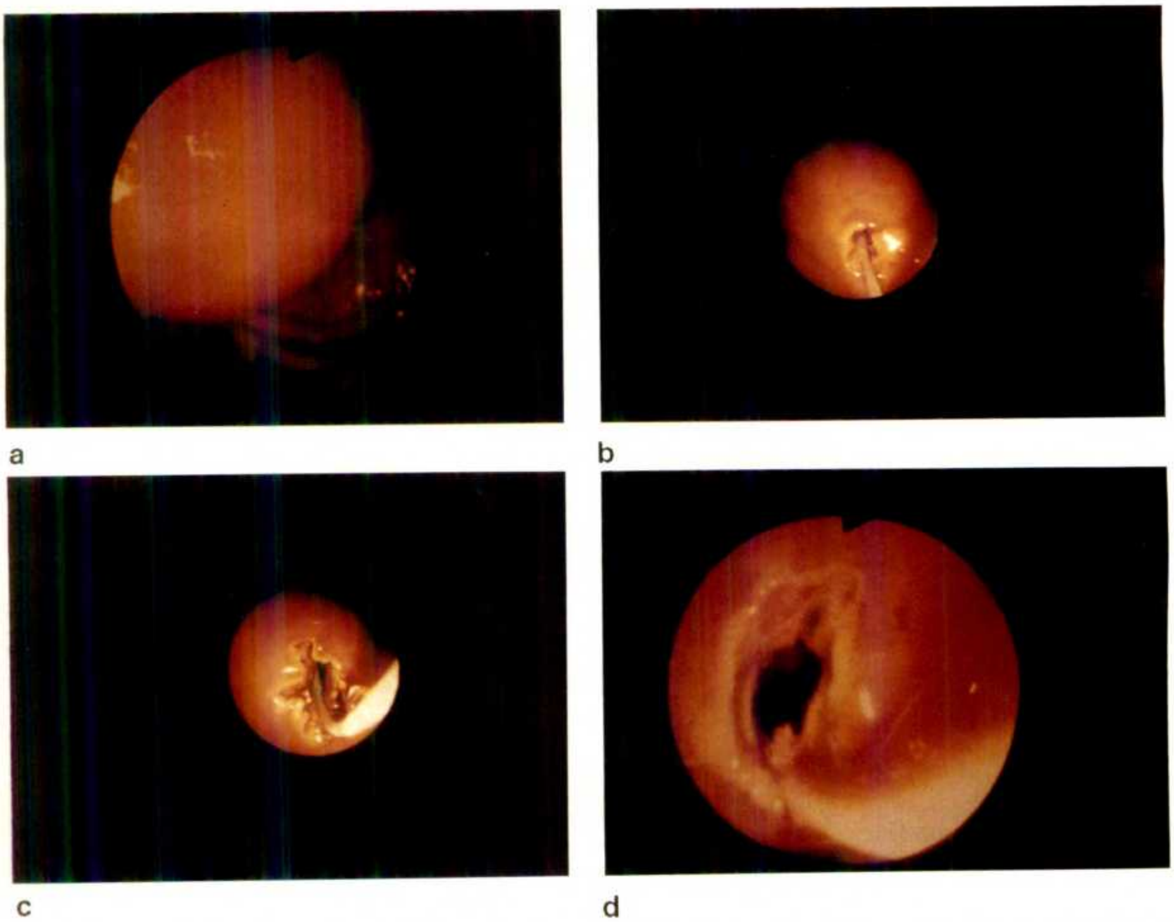

Fig. 2 **a** Pseudocyst seen bulging into the duodenal lumen; **b** needle knife incision into pseudocyst; **c** sphincterotome being used to extend the incision; and **d** final appearance of endoscopic cystduodenostomy

Newer modifications and techniques

Pancreatic abscess

Infected pseudocysts and abscesses are not a contraindication to endoscopic drainage. A number of successful cases have been reported of both transpapillary[12,13,40,41] and transmural[41] drainage using nasocystic catheters to wash out infected material under parenteral antibiotic cover.

Maisin *et al.*[42] described a patient with a thick (1 cm) pseudocyst/duodenal wall in whom ECD had been performed twice for a pancreatic abscess which, despite nasocystic drainage, still had inadequate drainage of the abscess. On a third ERCP the cystduodenostomy was seen to be patent but had partially closed. A 4·5-cm long, 10-mm diameter Z stent was placed which allowed improved drainage and complete resolution of the pseudocyst was confirmed by repeat ERCP and computed tomography at 1 year. The Z stent could not be removed and was left without complication.

Endoscopic ultrasonography and localizaton techniques

Endoscopic ultrasonography allows confirmation of the position of the pseudocyst in relation to the gut lumen and use of the linear-array Doppler facility has been advocated as a means of preventing haemorrhage in transmural drainage[32,43]. However, in two large series in which such ultrasonography was used to search for wall vessels[11,13], there were four instances of major bleeding, requiring surgical intervention in three patients. So, despite optimistic case reports, endoscopic ultrasonography has not resulted in lower vascular complication rates. There is, however, no doubt that the technique allows optimal visualization of the site of puncture and it may extend the application of endoscopic drainage by permitting drainage of cysts that do not cause an obvious bulge into the gut lumen. Experience is so far limited to a few case reports[38,39].

Confirmation of pseudocyst position and identification of the optimal site for transmural drainage may also be assisted by puncture of the pseudocyst with a standard needle catheter and injection of radio-opaque contrast under fluoroscopic control before incision of the wall[13,19,21]. This also allows aspiration of pseudocyst fluid for culture and cytological analysis where necessary. Using this technique Howell *et al.*[21] successfully drained seven of eight patients, most of whom had acute pancreatitis-related pseudocysts. Two patients were treated endoscopically in whom no visible bulge was seen on endoscopy by probing with the needle before needle knife incision. The authors also avoided two possible perforations by noting extravasation between the pseudocyst and the gastric wall, and abandoning the procedure. Both patients were successfully treated endoscopically at a later attempt. They also avoided one possible haemorrhage by noting contrast flowing within a large gastric wall vein and repositioning the drainage site.

Laser cystogastrostomy

Delmotte and colleagues[44] used an argon laser applied through a modified fibre in direct contact with the gastric mucosa to produce a small-calibre cystogastrostomy, with success in four patients. Buchi *et al.*[45] used a neodymium yttrium–aluminium–garnet (NdYAG) laser to produce a 1·5-cm diameter full-thickness burn in the gastric wall overlying the pseudocyst which necrosed and discharged spontaneously within 24 h. Irvine *et al.*[46] also used the NdYAG laser to create a circle of 5–10 small cystoenterostomies, which resulted in necrosis of the central 5-cm disc over 2–3 days, creating a very large cystogastrostomy. Both patients had large pseudocysts associated with acute pancreatitis. None of the seven patients treated by laser ECG has had any postoperative complication attributable to the procedure and there have been no recurrences in the short follow-up period reported. Interestingly, in Irvine's series[46] repeat endoscopy showed healing of the 5-cm ECG within months of the procedure.

Role of endoscopic treatment in relation to other available techniques

There are now a number of therapeutic options currently available for the management of pancreatic pseudocysts. Several algorithms have been suggested, with most authors recommending ERCP as a prerequisite to surgery[1,47,48]. Endoscopic drainage may be performed at the same time and, when biliary obstruction secondary to pseudocyst compression or chronic pancreatic obstruction is present, this may also be relieved by temporary stenting of the common bile duct[12,21,24,31].

Surgical options include internal or external drainage. External drainage is associated with a mortality rate of 6 per cent and a recurrence rate of 22 per cent[49]. This reflects its predominant usage in the management of complex cases, such as ruptured pseudocyst associated with acute pancreatitis, gross infection and haemorrhage; 10–29 per cent will develop an external fistula[50,51]. Internal drainage by cystogastrostomy, cystoduodenostomy or Roux-en-Y cystojejunostomy has been the mainstay of surgical treatment. In two collective reviews of 1280 and 986 patients respectively[49,52], the mortality rate was respectively 5 and 6 per cent (range 0–10 per cent), with a complication rate of 25 per cent and recurrence rates of 0–17 per cent. Complication rates are higher for cystogastrostomy than cystojejunostomy[1,53,54], as are recurrence rates[1,55,56].

Percutaneous aspiration of pseudocysts may be done under local anaesthesia or sedation, but this was associated with an unacceptably high rate of recurrence of 63 per cent and overall failure rate of 54 per cent in a collected series of 46 patients[52]. Continuous catheter drainage yields more impressive results, with a failure rate of 19 (range 8–33) per cent among 195 patients in seven studies[52]. However, the mean length of catheter drainage was 21 (range 9–58) days and the procedure is not without morbidity with a 16 per cent complication rate. The mortality rate is low but there were five deaths (3 per cent) overall. Prolonged catheter drainage is required when there is communication with the main pancreatic duct, with a mean of 28 days in the largest study[57]. Six of 34 patients subsequently developed an external fistula requiring surgery. Recently, internalization of the percutaneously placed stent by gastroscopic assistance has been reported with good success[58,59]. Larger series and long-term assessment are required.

The most recent treatment option to be developed is laparoscopic[60,61], and combined laparoscopic and endoscopic[62] procedures for pseudocyst drainage. So far, experience has been confined to isolated case reports with limited follow-up and its role remains to be established.

Cystic neoplasms may be mistaken for pseudocysts and inappropriately drained, delaying their diagnosis[2]. Particular care should be taken in patients presenting with cystic pancreatic masses in the high-risk group of young women, without a significant history of alcohol intake or gallstone disease, and without the classical pain of pancreatitis.

Conclusions

Endoscopic drainage offers a minimally invasive approach in selected patients with pancreatic pseudocysts associated with chronic pancreatitis. All three endoscopic techniques provide good results with high technical success rates, low recurrence rates and low morbidity. Recurrence rates appear comparable to internal surgical drainage with a lower morbidity and mortality rate. Restriction of the technique to patients with chronic pseudocysts with walls less than 1 cm thick will reduce the incidence of complications. ECG is associated with the highest complication rates and should be undertaken with caution and in a unit where appropriate surgical help is available. The risk of significant perforation may be further reduced by the use of localization techniques, but so far endoscopic ultrasonography has not reduced the risk of significant bleeding requiring surgery which occurs in 4·8 per cent (eight of 166) of all transmural drainage procedures (3 per cent of ECDs, 7 per cent of ECGs). The major limiting factor to the wider application of these techniques is availability of individual skills and institutional resources.

Endoscopic, internal surgical and percutaneous catheter drainage are not approaches which need to stand alone; patients may require treatment by more than one method. Emphasis has been placed on searching for a universally applicable approach[52]. We believe that more effort should be directed at identifying those patients who can be treated best by minimally invasive procedures and those who require open surgical procedures. Most studies have failed to acknowledge the heterogeneity of pseudocysts and have omitted to separate the outcome data of pseudocysts associated with acute and chronic pancreatitis It is now apparent that the pathogenesis, progression and treatment of acute and chronic pseudocysts are different[1,2], and studies should differentiate between these aetiologies in their analysis. Endoscopic drainage should be the treatment of choice where the anatomical situation is favourable in patients with chronic pancreatitis. The required anatomical juxtaposition for endoscopic drainage occurs in at least 50 per cent of pseudocysts associated with this disease. TCD is the safest procedure and is appropriate when there is communication of the cyst with the main pancreatic duct (around 50 per cent). Transmural drainage is applicable to pseudocysts in the head or body of the pancreas when the pseudocyst is visibly bulging into the gastrointestinal lumen (approximately 55 per cent). Long-term results are awaited to determine more accurately the place of endoscopic pseudocyst drainage in patients with ductal morphological changes who would previously have undergone more extensive surgical drainage procedures.

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Review

Management of gallstones in pregnancy

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Background Biliary disease during pregnancy is rare and the management of cholecystitis during pregnancy is controversial. Cholecystectomy in the pregnant patient has generally been avoided because of the reported high incidence of associated fetal loss. Recent developments relating to diagnostic and anaesthetic management have altered the overall approach to symptomatic biliary tract disease in pregnant patients.

Methods The literature was reviewed using Medline searches for cholelithiasis in pregnancy, to include pathophysiology, diagnosis and management.

Results and conclusion Surgery should be performed only for complicated non-resolving biliary tract disease during pregnancy as in over 90 per cent of patients the acute process will resolve with conservative management. For patients requiring operative intervention, laparoscopic cholecystectomy has emerged as a safe and effective method of treatment.

After appendicitis, cholecystitis is the commonest general surgical condition encountered during pregnancy[1]. Cholecystectomy is required during one to eight of every 10 000 pregnancies[2,3]; it may result in prematurity, spontaneous abortion, perinatal mortality, and maternal morbidity and mortality[4]. Controversy continues as to the safest management of symptomatic cholelithiasis during pregnancy[5]. Medical treatment of acute cholecystitis may be prolonged and result in recurrent hospitalization, whereas surgical management exposes the mother and fetus to the inherent risks of surgery and general anaesthesia[6]. The pathogenesis and management of cholelithiasis in pregnancy are reviewed; the indications for and optimal timing of surgical intervention are discussed with particular emphasis on the emerging role of laparoscopic surgery.

Effects of pregnancy on gallbladder and biliary lipid secretion and composition

Several studies have shown that multiparity is associated with an increased risk of developing gallstones[5,7,8]. In 1968 Glenn and Meshny[9] reviewed 218 cholecystectomies in young women and reported that 81 per cent had developed biliary symptoms within 1 year of onset of pregnancy. This increase in the incidence of gallstones, which starts at puberty and decreases after the menopause, suggests that gallstone formation may be mediated by changes in oestrogen or progesterone levels[10,11]. Numerous studies have confirmed that oral contraceptive use is associated with an increased incidence of gallbladder disease. A number of investigators have shown that, after an overnight fast, bile is significantly more saturated with cholesterol in women using oral contraceptives than in those not taking such agents[12–14]. Wingrave and Kay[15] demonstrated that the risk of developing gallstones associated with the use of contraceptives is short term. However, newer contraceptives with a very low component of oestrogen do not have any effect on the formation of gallstones[16].

Several studies have indicated that there is abnormal gallbladder motility during pregnancy. In 1935 Riegel *et al.*[17] found evidence of impaired fluid absorption in pregnant women at full term. In 1938 Gerdes and Boyden[18] showed radiological evidence of impaired gallbladder emptying. Further radiological studies have been limited by reluctance to expose pregnant women to the risks of radiation. In 1980 Braverman *et al.*[19] used real-time ultrasonography to evaluate gallbladder kinetics in pregnant women and contrasted the findings with those in non-pregnant controls. After the first trimester of pregnancy, gallbladder volume during fasting and residual volume after contraction were twice as large in pregnant patients as in controls. The rate of emptying and the percentage emptied were also reduced. Incomplete emptying of the gallbladder in late pregnancy leaves a large residual volume and may cause retention of cholesterol crystals, a prerequisite for cholesterol gallstone formation. Several mechanisms may explain these changes in gallbladder function during pregnancy. Increased fasting gallbladder volume might be due to decreased absorption of water from the gallbladder mucosa. This could be related to high concentrations of oestrogen, which have been shown to decrease the activity of the sodium pump in the gallbladder mucosa[20]. Progesterone may impair gallbladder contraction by inhibiting cholecystokinin-mediated smooth muscle contraction, which is the primary regulator of gallbladder contraction. It is also reasonable to speculate that progesterone acting similarly may reduce the responsiveness of the gallbladder to cholecystokinin[21,22]. In the sluggish gallbladder, sequestration and precipitation of cholesterol or calcium salts of bilirubin may occur.

Studies measuring biliary lipid secretion and composition have provided evidence for the formation of gallstones during pregnancy. Carter[23] measured postprandial venous plasma levels of total bile acids and found low, but progressively increased, levels during pregnancy. Kern *et al.*[24] examined duodenal fluid after fasting and following gallbladder stimulation in non-obese healthy pregnant and non-pregnant women, and evaluated biliary lipid composition and secretion. Bile was found to be

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more saturated with cholesterol in the second and third trimester. This supersaturation suggests that pregnancy does increase the risk of forming gallstones.

An increased rate of secretion of cholesterol relative to bile acid and phospholipid secretion in the last two trimesters has also been shown[25]. This is consistent with the secretion of a more lithogenic bile There is also a decrease in the proportion of chenodeoxycholic acid with an increase in that of cholic acid. There is evidence that the individual primary bile acids have different effects on the coupling of cholesterol and phospholipid to bile acids and, therefore, these changes in bile acids may be a factor in making the bile more lithogenic[24]

Cholelithiasis in pregnancy

The incidence of gallbladder disease during pregnancy ranges from 0·02 to 0·3 per cent[26–33]. This rate does not exceed that in non-pregnant women of the same age group[26 32,34]. The clinical picture of cholelithiasis is no different from that in the non-pregnant woman. Pain occurs in the right upper quadrant or epigastrium radiating to the back and reaching a peak within 12–24 h. In more than 50 per cent of patients with stones, a history of previous fatty food intolerance can be elicited. In severe cases, empyema of the gallbladder may result, and a mass may be palpable[26] Jaundice occurring in pregnancy is due to common duct stones in 7 per cent, hepatitis in 42 per cent and cholestasis in 20 per cent of patients[1]. The incidence of pancreatitis during pregnancy ranges from one in 2000 to one in 10 000 pregnancies[1 35 36], with cholelithiasis as the most common aetiological factor[37] Unlike cholecystitis, pancreatitis has been associated with a significant maternal mortality rate (15–60 per cent)[1 26 30 36 38] and a fetal mortality rate approaching 60 per cent[1 30 31] Ultrasonography has greatly enhanced the ability to diagnose gallbladder disease safely and accurately in pregnancy[39]; accuracies of over 90 per cent have been reported regularly[40 41]

Management of symptomatic cholelithiasis in pregnancy

Conservative management

Most clinicians agree that surgery is indicated for those with repeated attacks of biliary colic, acute cholecystitis, obstructive jaundice, gallstone pancreatitis, peritonitis or uncertainty in diagnosis[7 8 28 40]. However, owing to the high incidence of fetal loss secondary to cholecystectomy (*Table 1*), the treatment of choice for uncomplicated cholecystitis during pregnancy is non-operative, with elective cholecystectomy performed after delivery[28,32 42,43,45]. Even surgeons who advise aggressive treatment advocate conservative management during the first and third trimester[1,5,28,30,31,33,44,46,47]. The weight of published opinion before 1987 favoured primary non-operative management of symptomatic cholelithiasis during pregnancy (*Table 1*).

In the majority of patients conservative management of cholecystitis in pregnancy is successful. Hamlin *et al.*[48] reviewed the experience at the Massachusetts General Hospital and found that in 23 patients the symptoms of cholelithiasis subsided promptly on conservative management and all patients went to term uneventfully. In more than 90 per cent of cases the acute process resolves, but subsequent repeated attacks may require surgery[26]. Swisher *et al.*[33] have shown that acute cholecystitis responds less well to conservative management than either biliary colic or gallstone pancreatitis during pregnancy.

Dixon *et al.*[44] reviewed 26 patients with biliary colic during pregnancy who were treated without operation Fifteen patients suffered recurrent episodes of biliary colic during the course of the pregnancy. Of these 15 patients, eight were hospitalized once, five were hospitalized twice and two were hospitalized three times. Two patients underwent preterm induction of labour which allowed earlier surgery to relieve persistent symptoms unresponsive to medical treatment. Two patients required treatment with total parenteral nutrition for 27 and 30 days for intractable symptoms that occurred in the third trimester; one of these patients also developed gallstone pancreatitis. Spontaneous abortion occurred after onset of biliary tract symptoms in three of the 26 patients at 7, 12 and 14 weeks of gestation. Abortion was induced in three patients during the first trimester because of persistent or recurrent symptoms and the desire for early cholecystectomy.

Swisher *et al.*[33] reviewed 72 pregnant women who presented with symptoms of biliary disease. Sixty-one patients (85 per cent) were successfully treated conservatively at the initial presentation but 40 (66 per cent) subsequently developed recurrent symptoms. Four patients (6 per cent) went into premature labour secondary to biliary disease and were successfully managed with tocolytic agents. Five patients (7 per cent) underwent emergency cholecystectomy. Six patients (8 per cent) required induction of labour in an attempt to decrease the severity of the disease. No maternal or fetal death occurred following medical or surgical management.

McKeller *et al.*[28] reviewed 22 pregnant patients requiring admission for symptomatic cholelithiasis. Sixteen were admitted once for gallbladder disease during pregnancy, three were admitted twice and two were

Table 1 Results of cholecystectomy during pregnancy by trimester

		Abortion per no. of cholecystectomies			Premature labour per no. of cholecystectomies		
Reference	Year	Trimester I	Trimester II	Trimester III	Trimester I	Trimester II	Trimester III
Green *et al*[42]	1963	2 of 10	2 of 5	0 of 2	0 of 10	0 of 5	0 of 2
Printen *et al.*[31]	1978	2 of 2	0 of 4	0 of 0	0 of 2	0 of 4	0 of 0
Hiatt *et al*[40]	1986	5 of 7	1 of 5	0 of 12	0 of 7	0 of 5	0 of 12
Landers *et al*[43]	1987	3 of 3	0 of 3	0 of 3	0 of 3	0 of 3	2 of 3
Dixon *et al*[44]	1987	3 of 3	0 of 12	0 of 1	0 of 3	0 of 12	1 of 1
Total		15 of 25	3 of 29	0 of 18	0 of 25	0 of 29	3 of 18

Eleven patients sought elective abortion because of unwanted pregnancy admitted three times. One patient was admitted four times before having surgery. There were no maternal or fetal deaths in either the operative (nine patients) or non-operative group.

Open cholecystectomy during pregnancy

The severity of the surgical disease and not the surgery itself appears to be the more important factor in determining prematurity, spontaneous abortion, perinatal mortality, and maternal morbidity and mortality from symptomatic gallstone disease during pregnancy. Maternal and fetal morbidity and mortality is particularly low for a planned cholecystectomy carried out in the second trimester[1]. Kammerer[1] reviewed a large series of patients suffering non-obstetrical surgical problems during pregnancy and found no significant increase in perinatal mortality in this group of patients. The incidence of prematurity and fetal loss increased substantially, however, with increasing severity of the underlying surgical disease[1]. Following uncomplicated cholecystectomy, there is no increase in maternal mortality, and the rate of fetal loss is approximately 5 per cent[1,31,36]. However, when pancreatitis complicates cholelithiasis during pregnancy, cholecystectomy is associated with a maternal mortality rate of up to 15 per cent and fetal loss of about 60 per cent[31–36]. Hiatt *et al.*[40] reported fetal salvage in only 20 of 26 pregnant patients presenting with acute biliary tract disease. Nine patients underwent cholecystectomy because of failure of conservative management, and fetal loss occurred in five (two spontaneous abortions, two therapeutic abortions and an unsuspected ectopic pregnancy) of the nine patients. Another patient had a therapeutic abortion before cholecystectomy. Thus six fetuses were lost in 26 patients, five in the first and one in the second trimester. Hiatt and colleagues[40] reasonably concluded that operative treatment for symptomatic cholelithiasis during pregnancy should be delayed.

Dixon *et al.*[44] reported a series of 44 pregnant patients with symptomatic biliary disease. Three of 26 patients managed conservatively had a spontaneous abortion Fourteen patients underwent cholecystectomy during the second trimester; 12 delivered healthy infants and two were lost to follow-up. Three patients in this series were not known to be pregnant while undergoing cholecystectomy during the first trimester. Elective abortion was induced in two of the patients because of exposure to radiation during diagnostic evaluation and a third patient sought abortion because of unwanted pregnancy.

Recent reports of open cholecystectomy during pregnancy have demonstrated a favourable outcome[28,33,49,50]. McKeller *et al.*[28] reported nine cholecystectomies performed during pregnancy; two patients were operated on during the first trimester, four during the second and three during the third. Two patients underwent premature contractions which were easily controlled with tocolytic agents. There were no fetal deaths. Swisher *et al.*[33] reported 16 cholecystectomies in pregnant women, five in the first trimester and 11 in the second. No perioperative fetal or maternal death was reported. Two patients developed premature contractions which were controlled successfully with tocolytic agents. Percutaneous cholecystostomy under local anaesthesia has been described as an effective management option for biliary disease in pregnancy[49,50]. The procedure avoids the inherent risks of surgery and anaesthesia for mother and fetus but it is not performed very often.

Laparoscopic cholecystectomy during pregnancy

When laparoscopic cholecystectomy was first introduced, pregnancy was cited as an absolute or relative contraindication to the technique[51,52]. However, several recent studies have documented its successful use during pregnancy[5,30,46,47,53–68]. In 1995 Lanzafame[5] reviewed 20 reports of such treatment, and a further three reports of 14 patients who underwent laparoscopic cholecystectomy during pregnancy without any fetal or maternal mortality[69–71] have been published since then. *Table* 2 summarizes the outcome for 60 patients; although most were operated on during the second trimester ($n = 37$) those in whom laparoscopic cholecystectomy was performed during the first ($n = 4$) and third ($n = 6$) trimesters also completed their pregnancies uneventfully

The patient is placed in the reverse Trendelenburg position, the degree of which should be minimized as the gravid uterus may compress the vena cava. Morrel *et al.*[46] also recommend left lateral rotation of the operating table to displace the uterus from the vena cava. A facility for perioperative monitoring of the fetal heart and uterine contractions should be available[46]. Positioning of ports is no different from that in non-pregnant patients Most authors recommend initial trocar placement under direct vision (Hasson technique), either from below the umbilicus if the uterus is not very big or via the right upper quadrant lateral to the mid-clavicular line in the later stages of pregnancy. The remaining ports are introduced under camera vision[5]. A total of 14 patients underwent cholangiography in the collected series[46,47,56,57,61]. Although some surgeons performed cholangiography routinely[46,47,57], others favoured selectivity[56,61]. A single film should suffice and a lead shield should be placed over the lower abdomen to protect the fetus from radiation exposure. Conversion to open cholecystectomy should be undertaken promptly if intraoperative conditions make continued laparoscopic surgery hazardous[5].

Discussion

Cholecystectomy for symptomatic cholelithiasis is the second commonest non-obstetric operation carried out in the pregnant patient. Cholelithiasis is estimated to occur in 0·07 per cent of pregnancies, with approximately 40 per cent of these patients requiring operation[26,28]. Before 1985 most authors recommended a conservative approach where possible but, in the past 10 years, there has been a swing towards a more aggressive approach[44,72]. However, most still advise conservative treatment for the majority of pregnant patients. The morbidity and mortality rates following laparoscopic cholecystectomy during pregnancy compare favourably with those of open cholecystectomy[52,73]. The indications for surgery must be individualized but patients with repeated attacks of biliary colic, acute cholecystitis, obstructive jaundice, gallstone pancreatitis or uncertainty in diagnosis[7,8,28,40] are candidates for either cholecystectomy or, at least, cholecystostomy.

The timing of cholecystectomy in pregnancy remains controversial. McKeller *et al.*[28] found that the risk of spontaneous abortion decreased with gestational age. The risk was 12 per cent during the first trimester, 5·6 per cent during the second and 0 per cent during the third. They further noted that the incidence of premature labour was zero during the second trimester and 40 per cent during the third. Several authors recommend that surgery be performed during the second trimester of pregnancy,

Table 2 Results of laparoscopic cholecystectomy during pregnancy

Reference	Year	No. of patients	Trimester I	Trimester II	Trimester III	Tocolytics	Cholangiography	Spontaneous abortion	Preterm labour
Adamsen *et al.*[53]	1993	2	0	2	0	0	0	0	0
Arvidsson and Gerdin[54]	1993	1	0	1	0	0	0	0	0
Bennett and Estes[55]	1993	1	0	1	0	0	0	0	0
Chandra *et al*[56]	1994	1	1	0	0	0	1	0	0
Comitalo and Lynch[57]	1994	4	0	4	0	2	3	0	0
Constantino *et al.*[58]	1994	2	0	2	0	0	0	0	0
Csaba and Orban[59]	1994	1	0	1	0	1	0	0	0
Eldring[47]	1993	5	1	3	1	0	5	0	0
Fabiani *et al.*[60]	1993	1	0	1	0	0	0	0	0
Hart *et al.*[61]	1993	3	1	2	0	0	1	0	0
Jackson and Sigman[62]	1993	1	0	1	0	0	0	0	0
Lanzafame[5]	1995	5	0	3	2	2	0	0	0
Morrel *et al*[46]	1992	5	0	3	2	0	5	0	0
Pucci and Seed[63]	1992	1	0	0	1	0	0	0	0
Rusher *et al*[50]	1993	1	0	1	0	0	0	0	0
Schorr[64]	1993	2	0	2	0	0	0	0	0
Shaked *et al.*[65]	1994	1	1	0	0	0	0	0	0
Soper *et al*[66]	1992	6	0	6	0	0	0	0	0
Weber *et al*[67]	1991	1	0	1	0	0	0	0	0
Wilson *et al.*[68]	1994	2	0	2	0	0	0	0	0
Sigman[71]	1995	1	0	1	0	0	0	0	0
Prinz[70]	1995	3	—	—	—	—	—	—	—
Ronaghon[69]	1994	10	—	—	—	—	—	—	—
Total		60	4	37	6	5	15	0	0

because organogenesis is complete (at 12 weeks), the uterine size is not large enough to interfere with the operative field and the risk of spontaneous abortion is low[46,47,50,57,61,73].

Laparoscopic cholecystectomy during pregnancy appears to be safe[74,75]. None of the 60 cases reported in the literature was associated with either perinatal or maternal mortality. However, the effects of prolonged carbon dioxide pneumoperitoneum on fetal physiology remain largely unstudied, and perioperative fetal monitoring is mandatory; Hart *et al.*[61] advocate transvaginal ultrasonography as the most efficient means of intraoperative monitoring. Some authors advise perioperative monitoring of both fetal heart rate and uterine contractions[46]. While general anaesthesia is the norm for laparoscopic cholecystectomy, Constantino *et al.*[58] have reported a patient in whom the procedure was successfully performed under epidural anaesthesia. They recommend that such anaesthesia be considered for the safety of fetus and mother.

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Review

Prognostic factors in gastric cancer

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Background Despite gastric cancer being common, its prognosis has not been improved significantly in recent years. Now, greater insight has been gained into the biological properties of tumour cells, how they become malignant and what mechanisms they may use to invade and metastasize. This involves tumour-associated protease systems, loss or mutation of adhesion molecules and changes in genetics. The view of gastric cancer is changing: it is not only a solid tumour but also exhibits a minimal residual disease component even in the early stages of disease. Such biological tumour characteristics may provide new prognostic factors and also potential new therapeutic options.

Methods This is an update of prognostic factors in gastric cancer, emphasizing new biological features, some of which have been investigated by this group over the past few years. Current results are discussed in the light of 212 references obtained from the Medline database from 1979 to 1997.

Results There is high probability that some of the factors reviewed, such as c-*erb*B-2, individual course and phenotyping of disseminated tumour cells will become significant new prognostic variables. This is true also, to a lesser extent, of cathepsin D, matrix metalloproteinase 2 combined with activators or tissue inhibitor of metalloproteinases 2, CD44, E-cadherin, p53 and *cripto*. Plasminogen activator inhibitor 1 (PAI-1), a member of the urokinase-type plasminogen activator (uPA) system, can already be defined as an established new prognostic factor in gastric cancer.

Conclusion PAI-1 should be considered prognostically in addition to established tumour classifications. Moreover, the uPA system is a target for future therapeutic concepts. Further analysis of factors describing tumour biology should lead to new, functionally orientated, tumour classifications in gastric cancer.

The overall outcome for patients with gastric carcinoma has not significantly improved over the past decade. Excluding early gastric cancer (with 5-year survival rates of about 80–90 per cent[1]) and gastric cancer in Japan (with about 70 per cent 5-year survival most probably owing to higher proportions of early-stage cancer and of curative resections[2]), the present chance of 5-year survival is estimated at 20 per cent[3] to 45 per cent[1,4]. With an incidence of between 22 and 30 per 100 000 European inhabitants[1,5], however, gastric cancer still holds its position as one of the most common cancer types in the world. In such a setting investigations into factors determining individual prognosis and the development of therapeutic concepts are of major importance.

Prognostic factors in cancer have many aspects[2]. At present, most serve to predict clinical outcome for individual patients, aiming especially at the identification of subgroups at high risk of relapse. In cancers with proven effective adjuvant treatment modalities, prognostic variables help to classify patients into therapeutic groups which statistically should benefit from adjuvant treatment protocols. Ideally, prognostic factors should also suggest options for therapeutic intervention. Unfortunately, in the case of gastric cancer the established prognostic factors have not reached this level of sophistication up to now. For instance, in contrast to breast cancer, adjuvant therapeutic strategies either have not been proved to be of significant benefit, or selection criteria for those patients who might benefit from adjuvant protocols have not yet been identified.

During the past decade efforts have been made to identify new prognostic variables. In contrast to almost all of the established factors, these variables were orientated at tumour biology, in a period when knowledge of tumour cell behaviour was increasing dramatically[6] (*Table 1*). To permit separation from the primary tumour and invasion of surrounding structures, tumour cells have been shown to downregulate the expression of adhesion molecules[7–9] and to overexpress complex tumour-associated protease and protease inhibitor systems. This effects the malignant criteria of invasiveness and metastasis[6,10–15]. Systemic spread of tumour cells may be demonstrated in the very early stages of solid cancers[16–25] and recently the authors have provided strong evidence for the biological autonomy of an early systemic disease component in gastric cancer[26]. Finally, outgrowth and establishment as distant metastasis are aided by proteolytic enzymes, but angiogenetic factors, growth factors and their receptors[27], and proliferative capacity are decisive in this context. Increasing numbers of investigations are being carried out on certain oncogenes, tumour suppressor genes and other molecular mechanisms[27–29].

This review is an update of prognostic factors in gastric cancer, with emphasis on new biological variables. These variables are more able than established factors to yield useful information about the biology of individual tumours. Potentially they promise not only more detailed and functionally orientated tumour classifications but also the possibility of individual therapeutic targets for the future.

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Conventional prognostic variables

The first section of the review briefly summarizes results associated with variables that are defined by the condition of the patient, the treatment and the morphology of the tumour. These classical variables have been studied in large multivariate analyses in the past.

Patient-related factors

Gastric cancer preferentially affects patients aged 50 years and over[1]. It also tends to affect more men than women[1,30] It has therefore been proposed that age and sex might be prognostic risk factors. In this regard the results of studies have been contradictory. Some multivariate analyses with more than 500 patients[4,31–34] have reported independent prognostic influence, others have not[35–39]. Female sex was reported to be associated with better prognosis in one study on R_0 (curatively resected) patients[40], and for certain subgroups in two other reports[35,41]. Other possible patient-associated factors, such as pattern of symptoms, weight loss, comorbidity and immune status, have not yet been demonstrated as independent significant factors in multivariate analysis. In summary, there is no definite consensus on the significance of patient-related variables as independent factors determining survival.

Table 1 Overview of steps of tumour invasion and metastasis and biological features correlated with them

Metastatic status	Potential parameters relevant
Primary tumour	Stroma induction/angiogenesis· protease inhibitors (PAI, TIMP) Growth and proliferation tyrosine kinase receptors (c-*erb*B-2, c-*met*), growth factors and their receptors (EGF receptor, *cripto*), signal transduction (c-*ras*), cell-cycle regulators (*pic1*, G1 and G2 cyclins, CDKs, *MTS*1), tumour suppressor mutations (*p53*, *nm23*), block of apoptosis (*bcl-2*), genetic instability
Segregation from the primary tumour	Loss of adhesion molecules, tumour-associated proteases/inhibitors
Invasion of surrounding tissue	Tumour-associated proteases (uPA system, MMPs, cathepsins and others)
Invasion of blood vessels	Tumour-associated proteases (uPA system, MMP-2, MMP-9 and others)
Systemic dissemination	Disseminated tumour cells (CK18 positive)
Adhesion and extravasation	Adhesion molecules, tumour-associated proteases
Establishment as metastasis	Interaction with microenvironment: tumour-associated proteases and inhibitors, adhesion molecules, loss of MHCI as immunological escape[200] Stroma induction/angiogenesis· protease inhibitors (PAI, TIMP) Growth and proliferation: tyrosine kinase receptors (c-*erb*B-2, c-*met*), growth factors and their receptors (EGF receptor, *cripto*), signal transduction (c-*ras*), cell-cycle regulators (*pic1*, G1 and G2 cyclins, CDKs, *MTS*1), tumour suppressor mutations (*p53*, *nm23*), block of apoptosis (*bcl-2*), genetic instability

PAI, plasminogen activator inhibitor; TIMP, tissue inhibitor of metalloproteinases; EGF, epidermal growth factor, CDK, cyclin-dependent kinase; UPA, urokinase-type plasminogen activator; MMP, matrix metalloproteinase; CK, cytokeratin; MHC, major histocompatibility complex

Treatment-related factors

There is no doubt that survival is decisively determined by the ability to perform macroscopically and microscopically complete surgical resection of tumour. Median survival time after non-curative resection (R_1 or R_2) has been reviewed[42] and ranges from 7 to 11 months; after explorative laparotomy or palliative gastroenterostomy it is 3–5 months. In contrast, median survival time after curative resection ranges from 35 to 75 months[2]. A curative tumour resection must still be recognized as the most powerful prognostic variable.

In addition, there is consensus that the quality of the resection is relevant to survival. Several studies have demonstrated especially that extended lymph node resection, including compartments I and II, performed without increased risk of perioperative morbidity, is associated with better long-term survival[11,34,43–46]. Siewert *et al.*[46] have demonstrated that radical lymph node dissection, defined as removal of 26 or more nodes, is an independent prognostic factor in patients with stage II and IIIA disease. There is also evidence that the hospital is an independent prognostic factor[31,32], with a higher probability of survival for patients operated in centres with a broad experience in oncological surgery.

Perioperative allogeneic blood transfusion has an adverse effect on the immune response, inducing a higher risk of postoperative infection[47] and, potentially, supporting the establishment of minimal residual tumour disease[48]; an association with poorer survival in gastric cancer has been reported[48,49], but the independent influence of allogeneic blood on survival still remains to be shown.

No advantage could be shown for adjuvant chemotherapy after curative tumour resection in terms of longer disease-free or overall survival time[1,50]. This can also be stated for a combination of chemotherapy (5-fluorouracil (5-FU) fluorouracil adriamycin metiotrexate (FAM)) and radiation therapy, adjuvant radiation therapy or intraoperative radiation therapy[1,51,52]. Randomized trials evaluating the prognostic value of defining patient subgroups profiting from neoadjuvant chemotherapy have to be performed[53]. Neoadjuvant chemotherapy may potentially increase survival mainly by increasing the chance of curative resection in advanced stages of gastric cancer. Indeed, there have been studies[1,54,55] in which resection rates between 62 and 93 per cent, including 71–100 per cent R_0 resections, could be achieved. However, the results of such studies are difficult to interpret as they were non-randomized and the criteria for non-resectability of treated cancers were not standardized.

There is still controversy regarding chemotherapy for non-resectable advanced gastric cancer. However, in recent years new combinations of chemotherapeutic agents with acceptable monoactivity in gastric cancer (which means objective remission rates of about 20 per cent) have been developed, such as methotrexate, 5-FU and adriamycin (FAMTX); adriamycin, cisplatin and etoposide; leucovorin, 5-FU and etoposide; leucovorin; and 5-FU[56–58]. Such therapy may reach 40–50 per cent objective remissions, including 10 per cent complete remissions. A randomized study comparing FAM and FAMTX revealed significantly higher remission rates and significantly longer median survival in patients treated with FAMTX[59]. Modern chemotherapy of non-resectable advanced gastric cancer must therefore be assumed as influencing prognosis.

Established tumour-related factors

There is general consensus that the anatomical extent of gastric cancer is an independent prognostic variable. This has been shown for local infiltration depth (pT), nodal involvement (pN) and distant metastasis (M)[60–63]. In addition, the number of affected lymph nodes is associated with survival[2,61,64]. There is also a correlation between tumour site and survival, with proximal carcinomas (gastro-oesophageal junction, cardia, upper third of the stomach) associated with poorer survival[65,66]. Some studies report an independent prognostic impact for this variable[31,36,65,67].

For none of the existing histological classifications (World Health Organization[68], Laurén[69], Ming[70]) has an independent influence on prognosis been demonstrated up to now[2,63,71,72]. For tumour cell differentiation (G), results are controversial. Multivariate prognostic relevance of tumour cell dissociation at invasion fronts was reported by Gabbert *et al.*[73], and Nakane *et al.*[67] demonstrated a significant prognostic impact of grading. Other studies did not find an association with prognosis[4,35,36,63,65,74].

Lymphangiosis carcinomatosa has been noted as an independent prognostic factor in some larger studies[73,75]. In the authors' own study of 203 patients, a significant impact was revealed especially for disease-free survival[63,74]. Other investigators have not observed this[36,40,76]. Invasion of blood vessels by tumour cells may also correlate independently with poorer survival[40,75], but not all agree on this[36,63,76]. Contradictory results have also been obtained for Borrmann's macroscopic gastric cancer classification[36,38,63,67,76] and so it cannot be considered as an established prognostic variable.

Tumour markers

Measurement of the serum tumour markers, carcinoembryonic antigen (CEA), CA 19-9 and CA 72-4, has become standard as an indicator of relapse during follow-up after gastric cancer resection. Correlation with prognosis has been reported for perioperative levels of these serum markers, and also for CA 125, Sialyl Tn antigen, ST-439 and α_1-fetoprotein[77]. Independent prognostic influence has been shown for CEA[67,68] and CA 19-9[79]. However, the strongest impact is now ascribed to the combination of CEA and CA 72-4[80].

New functional biological variables

In recent years more insight has been gained into the mechanisms that underlie the ability of tumour cells to behave in a malignant fashion (*Table 1*). Some of the biological factors involved in these mechanisms have been investigated for their potential role as prognostic factors. The following is an overview of these functional factors.

Tumour-associated proteases and protease inhibitors

Tumour cell invasion and metastasis are biologically dependent on the proteolytic destruction of surrounding matrix components, including the basement membrane of vessels to enable the systemic circulation to be reached. Evidence has accumulated that this is achieved by a series of tumour-associated serine, aspartic, cysteine and threonine proteases, and metalloproteinases[6,10–15,81–83]. The proteolytic factors and specifically corresponding inhibitors employed by tumour cells, either by secretion or stromal induction, are different from physiological factors that play central roles in several remodelling processes: embryogenesis, fibrinolysis, inflammation, angiogenesis, wound healing[10–12,82]. However, investigations indicate that some of these protease systems are overexpressed in tumours and that tumours with a high level of proteolytic activity are more invasive than others[10,83–89]. This has been shown especially for the urokinase-type plasminogen activator (uPA) system, which includes the 55-kDa serine protease uPA, its specific cell membrane-bound receptor (uPA-R) and plasminogen activator inhibitor (PAI) 1 and 2 as specific inhibitors. uPA is able to induce destruction of a pattern of surrounding matrix elements by activation of plasminogen to active plasmin, and potentially directly to activate collagenase IV (matrix metalloproteinase (MMP) 2 and 9, see below) for basement membrane degradation[10–12,82]. In this way the uPA-R has a pivotal role as a concentrator of the activity of bound uPA, focusing proteolysis at tumour invasion fronts and so potentiating the effectivity of uPA[85,89,90]. The inhibitors, especially PAI-1, are essential for transcellular recirculation of uPA-R, guaranteeing a dynamic and flexible proteolytic system at the tumour cell surface[10,88]. Moreover, it is speculated that PAIs protect the inner part of a tumour or growing metastasis from self-destruction by overwhelming proteolysis, and are essential for the neoangiogenesis of outgrowing metastases[10,63,82,91].

In view of this association with tumour cell aggression, a potential role of the uPA system as a prognostic marker is suggested. Indeed, the prognostic relevance of this system has been studied and confirmed in many cancer types[92–98], revealing especially uPA and PAI-1 as independent prognostic variables. For gastric cancer the authors' group has demonstrated immunohistochemically with semiquantitative scoring that there is an overexpression of the uPA system[63,74]. Univariately, uPA, uPA-R and PAI-1 (but not PAI-2) were associated significantly with disease-free and overall survival (*Fig. 1*). In overall multivariate analysis, PAI-1 was revealed as a strong and independent prognostic variable[63]. These results corresponded exactly with a study by Nekarda *et al.*[99] performed on 76 patients with gastric cancer using an enzyme-linked immunosorbent assay. In another study on 160 gastric cancers[100], the significant association of the uPA system with prognosis was further confirmed. In a continuing analysis an especially strong and independent prognostic value of the uPA system was found in diffuse and poorly differentiated intestinal/gastric cancer[74], indicating the potentially similar biological behaviour of these types of tumour. Summarizing these results and considering similar observations for other solid carcinomas[92–98], the prognostic importance of the uPA system can be seen as a general principle in oncology, and PAI-1 can be considered as an established independent prognostic factor in gastric cancer.

The situation is different for the MMPs. The MMPs comprise a large family of zinc-dependent proteases which are capable of degrading different elements of stromal matrix (e.g. collagens, proteoglycans, laminin, fibronectin)[81] and are known to date to be inhibited by three different forms of tissue inhibitor of metalloproteinases

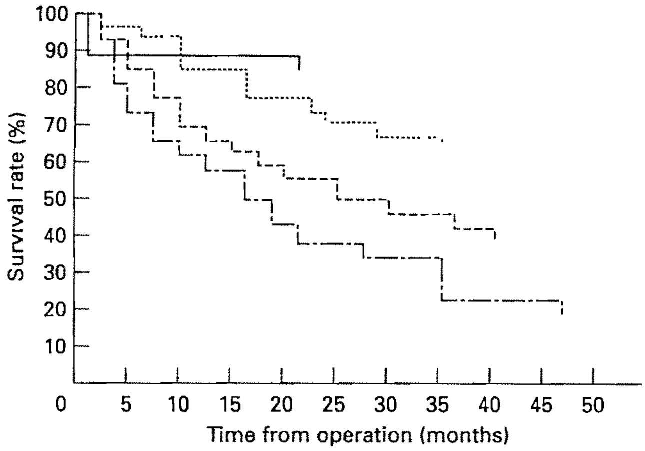

Fig. 1 Overall survival of 189 patients with gastric cancer according to immunohistochemical detection of plasminogen activator inhibitor 1 in tumour cells (semiquantitative score 0–3)[61]. Score 0 (———): eight patients, two events, mean survival time (MST) 44·5 months Score 1 (....): 46 patients, 14 events, MST 42·7 months. Score 2 (– – –): 74 patients, 38 events, MST 31·5 months Score 3 (— — · —): 61 patients, 39 events, MST 26 0 months. $P = 0\ 0019$ (Mantel–Cox test)

(TIMPs), TIMP-1, TIMP-2 and TIMP-3[83,101]. Large prognostic studies on MMPs and TIMPs in gastric cancer have not yet been performed, with the exception of MMP-2, the 72-kDa form of collagenase IV MMP-2 is capable of degrading the basement membrane component, collagen IV (besides collagen V, laminin and fibronectin)[83] and may be activated by uPA[11,82]. In contrast to the 92-kDa form of collagenase IV, MMP-9, it was postulated as a characteristic for the malignant phenotype in gastric tissue by Schwartz *et al.*[86], has been preferentially detected in advanced gastric cancers and correlates with vascular invasion[102]. Thus, an association with prognosis has been mooted. The authors have studied MMP-2 in a series of 203 patients, but only tendential univariate correlation with survival was detected and it failed as an independent parameter of prognosis (unpublished results). An association of MMP-2 with prognosis was noted in the subgroup of patients with high expression of uPA receptor. This probably indicates that MMP-2 is only of prognostic relevance if its activating proteases are overexpressed. A study by Grigioni *et al.*[103], moreover, indicates that the balance between MMP-2 and its inhibitor TIMP-2 could be of relevance. In summary, further prognostic studies on MMP-2, also considering co-expression of activating enzymes (e.g. membrane-type MMP) and inhibitors (TIMP-2) are necessary.

Another class of proteolytic enzymes located preferentially in lysosomes is the cathepsins. In particular, the oestrogen-inducible cathepsin D[104] has been investigated in breast cancer and there is consensus that raised tissue cathepsin D is a significant prognostic indicator of disease recurrence[105]. Cathepsin D is a lysosomal scavenger which plays an important role in intracellular protein metabolism, and in conversion of proenzymes and prohormones. The secreted enzyme is activated into a 34-kDa and 14-kDa dimer[105], and can degrade extracellular matrix components such as proteoglycans[106]. It further activates cathepsin B, which in turn activates uPA[82,107]. Moreover, a mitogenic activity has been mooted for cathepsin D[108]. In gastric cancer, strong immunohistochemical cathepsin D staining at advancing tumour margins has been reported[109], and it may have a role as a poor prognostic marker. However, an immunohistochemical study from Greece on 62 patients with gastric cancer (polyclonal antibody, chemotherapy in advanced stages) indicated an association with favourable prognosis[110]. The authors' group performed a prognostic study in a series of 203 patients using immunohistochemistry and a monoclonal antibody against cathepsin D. A significant association of cathepsin D in tumour cells was found with poorer disease-free and overall survival of patients who had curative resection (unpublished results). For disease-free survival, cathepsin D was an independent risk factor on multivariate analysis. As for MMP-2, there was a special prognostic relevance of cathepsin D in patients with parallel high expression of uPA-R, indicating that the aggressive potential of malignant tumours may derive from the concerted action of interacting proteolytic systems. With respect to other cathepsins (B, E, G), cathepsin B is also hypothesized to correlate with poor prognosis in gastrointestinal cancers[86,111]. However, no definitive large prognostic study on this factor in gastric cancer is available.

Observations that the prognostic relevance of MMP-2 and cathepsin D is improved when parallel high expression of the uPA system is taken into account prompt one to speculate on other protease systems that interact with this system The uPA system is subject to several interactions (*Fig.* 2), of which activation of plasminogen and MMP-2 by the uPA system and activation of uPA by cathepsins have already been discussed. Furthermore, α_2-antiplasmin and α_2-macroglobulin are inhibitors of active plasmin[82]. Besides its inhibitory function, α_2-macroglobulin may enhance transcellular circulation of uPA-R, mediated by a specific low density lipoprotein receptor-related protein/α_2-macroglobulin receptor[112–115]. This receptor is potentially necessary for internalization of uPA-R/uPA/PAI complexes and, in combination with PAI-1, for uPA-R recirculation[10,112,116].

Trypsin is a proteolytic activator of pro-uPA[82] and is inhibited by α_1-antitrypsin[117]. In contrast, chymotrypsin inactivates uPA-R by cleavage of one of the three uPA-R protein domains[88]. Thus, the chymotrypsin inhibitor α_1-antichymotrypsin is potentially protective to the uPA-R. Thrombin may proteolytically cleave uPA to an inactive enzyme form[82]. It is antagonized by antithrombin 3. However, antithrombin 3 is also able to inactivate uPA[118]. The tissue-type plasminogen activator (tPA) in analogy to uPA can activate plasminogen[82]. In contrast to uPA, overexpression or prognostic impact has not yet been shown for tPA[119–121].

Consideration of these interactive protease systems[122] has revealed an additional univariate prognostic impact of α_1-antitrypsin, α_1-antichymotrypsin and α_2-macroglobulin in the authors' series of 203 patients with gastric cancer and identified the combination of high expression of uPA-R, PAI-1, antichymotrypsin and α_2-macroglobulin as a high-risk protease pattern (unpublished results). As indicated above, all of the last three variables are essential for transcellular recycling of the uPA-R. From this it may be concluded that uPA-R recycling is of decisive importance for tumour cell aggression and prognosis in individual gastric carcinomas.

In summary, there is no doubt that tumour-associated proteases and inhibitors, and especially the uPA system, should be considered when predicting the prognosis of patients with gastric cancer. For the uPA system,

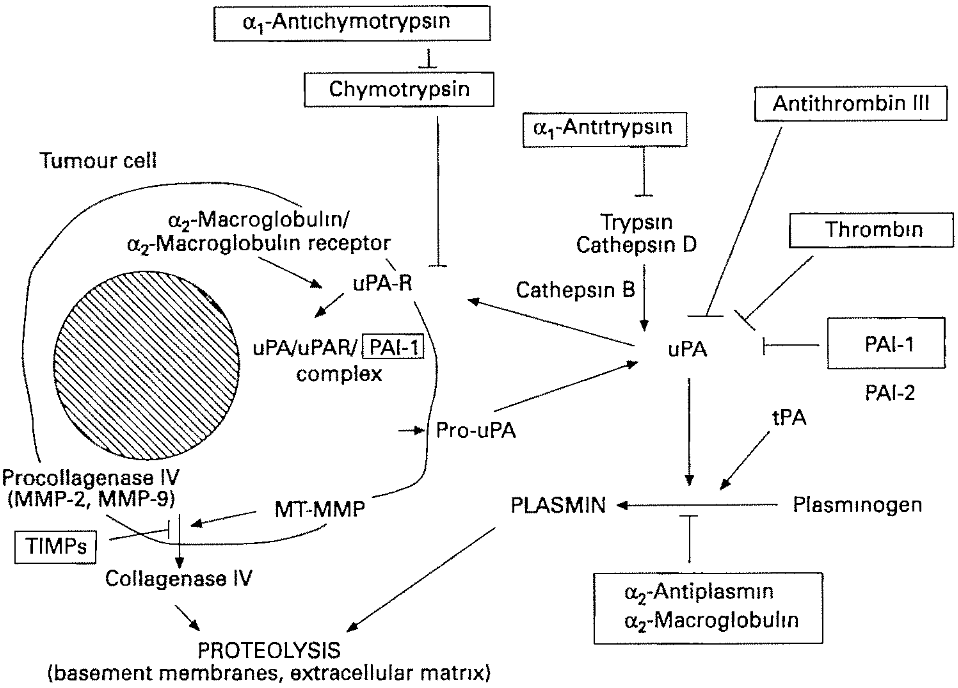

Fig. 2 Schematic overview of some of the multiple interactions of the urokinase-type plasminogen activator (uPA) system with other proteases/inhibitors Activation is shown by arrows and inhibition by bars (——|) with inhibitors in boxes. uPA-R, urokinase-type plasminogen activator receptor; PAI, plasminogen activator inhibitor; tPA, tissue-type plasminogen activator; MMP, matrix metalloproteinase, MT-MMP, membrane-type matrix metalloproteinase; TIMP, tissue inhibitor of metalloproteinases

emphasizing PAI-1, the authors believe that this factor characterizing the biology of tumour cells should be integrated into existing established tumour classifications.

Adhesion molecules

Recent studies on the mechanism of tumour metastasis indicate not only that an increase in proteolytic activity contributes to this process which characterizes malignancy but also that dysregulation of adhesion mechanisms increases the ability of tumour cells to detach from the primary site[7,123,124]. Downregulation of adhesion molecules is involved; these are classified into the cadherins, integrins, selectins, the hyaluronate receptor family including CD44, the sialomucin family, and the immunoglobulin superfamily including intercellular adhesion molecule (ICAM) and vascular adhesion molecule[7].

Perhaps the most conclusive experimental studies showing an association of downregulation with increase of metastasis have been carried out on E-cadherin[7]. E-cadherin is a 120-kDa, calcium-dependent surface glycoprotein which is expressed exclusively by epithelial cells[7]. It has been shown that invasive tumour cell lines have often lost E-cadherin[8] and that invasiveness of malignant cell lines can be reduced by transfection with E-cadherin complementary DNA[8]. On the other hand, antibodies against E-cadherin can induce the ability to invade collagen gels[124]. *In vivo*, downregulation of E-cadherin has been reported for various human cancers[125–129]. Nevertheless, adequate prognostic clinical studies on the expression of E-cadherin in gastric cancer are still missing. One immunohistochemical study[9] on 60 patients (31 who had curative resection) showed reduced expression of E-cadherin in 92 per cent of cases, significant correlation with dedifferentiation (G$_{3-4}$, Laurén diffuse type) and significant univariate association of low E-cadherin expression with disease-free and overall survival. An independent impact on prognosis, however, could not be shown.

A larger study of 125 patients with gastric cancer was performed by Yonemura *et al.*[130], also using immunohistochemistry. This investigation is interesting since E-cadherin staining is set in relation to staining for uPA in the same tumour series, and it has been hypothesized by Frixen and Nagamine[131] that loss of E-cadherin function potentially leads to upregulation of uPA. Correspondingly, Yonemura *et al.*[130] found an independent prognostic impact for uPA/E-cadherin status in their gastric cancer series, the worst prognosis being confined to uPA-positive and E-cadherin-negative tumours. However, as discussed previously, the prognostic relevance of the uPA system alone is very strong, and the multivariate results given for the combination of the parameters mentioned could result from a strong influence of uPA. Two further studies on E-cadherin in gastric cancer did not show multivariate impact[132,133]. In conclusion, prognostic impact of E-cadherin still has to be revealed in gastric cancer.

Another adhesion molecule which has been studied at some length in the context of cancer is CD44, a member of the hyaluronate receptor family[7]. It specifically binds to hyaluronic acid, is expressed by a wide range of cell types, and exists in a pattern of different isoforms generated by alternative splicing of messenger RNA and differential glycosylation[7]. These isoforms have in part lost the ability to bind hyaluronic acid as an extracellular matrix component[7]. Thus, abnormal transcripts and isoforms of CD44 have been suggested as playing a role in tumour invasion[134–138].

CD44 splice variants have also been detected in gastric cancer[134,139–141] and, from observation of different expression patterns of CD44 isoforms in Laurén diffuse and intestinal types, it has been speculated that these gastric cancer types may have different genetic pathways[134]. An immunohistochemical study[142] has indicated that CD44 is an independent prognostic factor in gastric cancer. However, this preliminary study showing univariate and multivariate prognostic significance of CD44 and its isoform CD44 9v was performed on 31 patients who had curative resection, with a mean follow-up time of 17 months. Investigations on the isoform CD44 9v were restricted to 22 of those patients and so further studies involving larger patient numbers are needed.

Involvement in tumour progression has been reported for adhesion molecules of the immunoglobulin superfamily (with architecture similar to that of immunoglobulins)[143]. A circulating form of ICAM-1 has been found at increased levels in those with cancer[144]. For the integrin family, very late antigen (VLA) 4, a molecule which is involved also in normal leucocyte traffic, is hypothesized to be used by tumour cells for haematogenous dissemination[7]. Of the selectin family, E-selectin has been shown to mediate carcinoma cell binding to endothelium[145] and thus could play a role in metastasis. However, there is no evidence so far that any of these factors may have an impact as prognostic variables in gastric cancer.

In conclusion, of the complex array of adhesion molecules no factor has yet been established as a definite new prognostic variable in gastric carcinoma.

Molecular variables

The rapid progress in molecular biology has given increasing evidence that transformation from a normal epithelial cell to a malignant cell is a multistep process and results from accumulation of multiple gene abnormalities[27–29,146]. Potentially, the patterns of overexpressed or down-regulated factors and enzymes described in the last two sections must be seen as the 'symptoms' of these genetic alterations. For gastric cancer, multiple gene alterations have been described, including oncogenes coding for tyrosine kinase receptors (including c-*met* and c-*erb*B-2), genes encoding growth factors and growth factor receptors (epidermal growth factor (EGF) receptor, *cripto*), genes involved in intracellular signal transduction (the *ras* family), regulators of the cell cycle, tumour suppressor genes (including *p53*, APC), genes preventing apoptosis (*bcl-2*) and genetic instability[28]. Alterations within these groups seem to occur in different patterns in well and poorly differentiated gastric carcinomas, so different genetic pathways are postulated for these differently differentiated stomach cancers[29].

Of the proto-oncogenes encoding tyrosine kinase receptors, the c-*met* gene encoding hepatocyte growth factor receptor has been shown to be frequently amplified in advanced gastric cancers[28,29,147,148]. Kuniyasu *et al.*[148] demonstrated significant correlation of expression of an aberrant transcript of c-*met* with tumour stage, lymph node metastasis and depth of tumour invasion. A prognostic value, however, has not yet been determined for this proto-oncogene.

In contrast, there is evidence that c-*erb*B-2 may be of significant prognostic value in gastric cancer; c-*erb*B-2 encodes a 185-kDa transmembrane glycoprotein with tyrosine kinase activity (p185), suggesting that this product is a potential growth factor receptor for an unidentified ligand[149–153]. One study even suggests that c-*erb*B-2 mediates tumour progression and metastasis by inhibiting expression of E-cadherin[28]. Amplification of c-*erb*B-2 has been observed preferentially in well differentiated gastric cancers[154–156]. Some clinical studies provide evidence of a role for this marker in survival analysis. An immunohistochemical study using a polyclonal antibody on 260 gastric cancers[157] found correlation with histological type, pN and serosal tumour invasion, and revealed significant univariate association of p185-positive tumours with poorer survival. This was also confirmed in a study by Uchino *et al.*[158] involving 108 patients which also used a polyclonal antibody and immunohistochemistry. Ten year survival of patients with p185-positive lesions of 37 per cent was significantly lower than the 91 per cent survival of those with p185-negative tumours. Yonemura *et al.*[159] and Jaehne *et al.*[160] found independent prognostic relevance of c-*erb*B-2 in series of 189 and 58 patients respectively. In the present authors' series of 203 patients, high expression of p185 protein was of independent prognostic impact (unpublished data). On the other hand, another immunohistochemical study[161] did not show p185 as a prognostic variable. In spite of this, there is overall strong evidence that c-*erb*B-2 might serve as a prognostic indicator in gastric cancer.

Of the growth factor and growth factor receptor gene family, it has been shown that overexpression of EGF receptors and EGF/transforming growth factor α receptors correlates with biological malignancy[162–164]. For gastric cancer, an autocrine stimulating pathway promoting tumour growth, cell division and even uPA/uPA-R expression has been suggested for EGF[165,166]. In particular, expression of *cripto*, a recently identified member of the EGF family, has been described as associated with gastric cancer[167,168]. Regarding prognostic relevance, there have been a few studies indicating that synchronous expression of EGF and EGF receptor in gastric cancer correlates with poor prognosis[169–171]; for expression of *cripto* an association with tumour stage and prognosis has been reported[168]. However, larger studies assessing the independent prognostic impact of these factors in multivariate analysis still remain to be done.

In intracellular signal transduction, the *ras* genes (N-*ras*, K-*ras*, H-*ras*) are assumed to play central roles, thereby also influencing cell proliferation and cell differentiation[27]. They encode proteins located to the inner layer of cell membranes, preferentially mediating signals of tyrosine kinase receptors by controlled guanosine 5′-triphosphatase (GTPase) activity[27]. Mutations of c-*ras* sites can eliminate the GTPase potential, leading to a permanent state of activation of the encoded RAS protein[27]. In gastric cancer, *ras* mutations have been detected[2,172,173], and a potential role in prognosis has been implicated[172]. However, this remains to be shown in large prognostic studies.

Of the group of cell-cycle regulators, *pic1* (p53-regulated inhibitor of cyclin-dependent kinases (CDKs)) and *MTS1* (encoding p16 protein) have been shown to be directly involved in cancer genesis[28]; *pic1* can be induced by the wild type of the tumour suppressor gene *p53*, but not by its mutants[174], and leads to direct inhibition of DNA replication, thereby preventing cells from entering the S phase[175]. Moreover, from experiments on gastric cancer cell lines *pic1* is hypothesized to suppress cdk2 and G1 cyclins[28]. Thus, mutation of *p53* or *pic1* can lead to overexpression of cdk2 and G1 cyclins, and to upregulated growth of gastric cancer cells. Correspondingly, overexpression of cyclin E has been reported in gastric cancers[28]. However, to the authors' knowledge there has been no prognostic study on *pic-1*, cdk2 or cyclin E in gastric cancer. The same can be said for mutations of *MTS1* which inhibits CDK4/cyclin D activity[176].

For the group of tumour suppressor genes, most prognostic studies in gastric cancer have been performed on *p53*. The wild-type form of p53 not only induces *pic1* as stated above, arresting the cell cycle in G1 and preventing cell-cycle progression into the S phase[175], but also induces apoptosis[175] after DNA damage[27]. Recent studies indicate that wild-type p53 regulates apoptosis in a manner that protects against malignant transformation[175]. In view of this, it becomes clear how loss of function of p53 by mutation can lead to transformation and/or tumour growth. Indeed in 60 per cent of gastric cancers, regardless of the histological type, allele loss and mutations on *p53* can be detected[28]. However, concerning the prognostic value of *p53* mutations in gastric cancer (mainly investigated immunohistochemically) there is no definite consensus. Mutant p53 proteins have been shown to accumulate within cell nuclei and, in contrast to wild type p53, have a prolonged half-life[177]. Thus, they can be detected immunohistochemically[178] at much higher probability than the wild type[177]. Nevertheless, the main difficulty in immunohistochemical studies is that most of the available antibodies to p53 proteins are not specific for mutant p53, but also bind to wild-type p53[177]. Of the available immunohistochemical studies, two demonstrated a univariate and multivariate significant impact of accumulation of p53 on survival in 125 and 206 patients respectively[179,180]. One study[181] confirmed shorter overall and disease-free survival in 55 patients. A recent report from Oiwa *et al.*[182] postulates an impact of p53 on prognosis in early gastric cancer because of a significant association with the penetrating A type[183]. Two other studies did not find a prognostic relevance of p53 accumulation[184,185]. A recent report from Gabbert *et al.*[186] of 418 patients also failed to describe an association of p53 expression with survival. These authors used a monoclonal antibody, however, which again recognized both mutant and wild-type p53. In conclusion, p53 cannot so far be regarded as an established prognostic factor in gastric cancer.

The expression of *nm23*, a suppressor gene for tumour metastasis and potentially tumour development[27,28,187] encoding nucleotide diphosphate kinase and PuF, a c-*myc* transcription factor[28], has been shown to be reduced in metastatic gastric carcinoma[188,189]. To the authors' knowledge, prognostic studies on *nm23* have not yet been introduced. Mis-sense mutations of another tumour suppressor gene involved in cell–cell adhesion, *APC*, are frequently detected in gastric cancers[28]. However, investigations on prognostic impact of *APC* mutations remain to be carried out.

The *bcl-2* gene encodes for a membrane-associated protein which blocks apoptotic cell death[27,190]. Ayhan *et al.*[191] demonstrated that loss of heterozygosity at the *bcl-2* gene locus could be detected in well differentiated gastric cancers in contrast to poorly differentiated ones. A prognostic role of *bcl-2* in gastric cancer has not been established up to now.

Finally, the concept is increasingly accepted that multiple genetic alterations affecting certain DNA sequences are involved in the development of malignancy. These regions are simple repeated sequences that are genetically unstable and prone to replication errors[192,193]. This genetic instability was detected at microsatellite loci particularly in poorly differentiated gastric cancers[194], in contrast to well differentiated tumours, suggesting a role for genetic instability in the genesis of poorly differentiated gastric cancer.

In summary, most evidence so far indicates a prognostic impact of c-*erb*B-2 and *p53* mutations in gastric cancer. However, the role of the latter in particular has still to be established definitely.

Minimal residual tumour disease

As a final new biologically defined prognostic variable in gastric cancer minimal residual tumour disease is proposed; this does not exist only in haematological malignancies[195,196], it is also suspected in solid cancers. Even in early stages of diverse carcinoma types, single disseminated tumour cells can be detected in the bone marrow compartment as cytokeratin (CK) 18-positive cells using immunocytochemistry[16–25,197–201]. This early systemic disease is mooted as the cause of the fatal clinical course of cancer, inducing recurrence months and years after and in spite of curative resection[26]. Disseminated tumour cells at the time of operation are significantly associated with clinical prognosis in diverse carcinoma types, including breast and colon cancer[16,20,21,24,202]. Disseminated tumour cells were detected before surgery in the bone marrow in 109 of 217 patients (57 per cent) resected for gastric cancer[17]. This has been corroborated by Juhl *et al.*[203], who found disseminated tumour cells in bone marrow and peritoneal washings in 25 of 48 patients. Nevertheless, the simple presence of these cells at the time of operation was not an independent prognostic parameter[17]. However, when the quantity of tumour cells was considered an independent impact on prognosis could be demonstrated.

To find further evidence of the biological autonomy of the systemic disease component in gastric cancer, sequential bone marrow aspirations were performed after curative surgery during follow-up of 78 patients[26]. The individual postoperative tumour cell course correlated significantly with later clinical outcome; 90 per cent of patients who later relapsed showed an increase in or constantly high numbers of tumour cells in bone marrow, whereas patients without recurrence had a reduction in or elimination of tumour cell numbers. An increase of five or more tumour cells in 10^6 6 months after curative tumour resection was a strong independent prognostic parameter[26].

As individual tumour cell courses in bone marrow appeared to be very heterogeneous, it was speculated that these cells were of varying biological and metastatic capacity[204,205]. In view of the association of the uPA system with aggressive tumour potential, an attempt was made to identify metastatic phenotypes by immunocytochemical double-staining for uPA-R[206]. A significant correlation was identified of uPA-R expression of disseminated tumour cells at the time of operation with later increasing tumour cell counts and survival[26,207].

In conclusion, it is suggested that minimal residual disease exists in gastric cancer with a high probability, that aggressive phenotypes of the disseminated cells can probably be identified by uPA-R analysis and that perioperative evidence of uPA-R on such cells might be a new biological prognostic variable. However, this hypothesis has to be verified in a larger series of patients.

Conclusion

Current results strongly suggest that tumour classification in gastric cancer will be extended by variables describing tumour biology. From the persuasive studies on the uPA system, performed not only in gastric cancer but also on several other cancer types[92–98], which all yield similar results, it can be stated that this tumour-associated protease system (and especially PAI-1) should be considered as an established new and independent prognostic factor in gastric cancer. It should therefore be considered in addition to established tumour classifications (defined by R category, pTNM, tumour localization, quality of tumour resection and hospital experience). Moreover, the authors believe that intensifying attempts to characterize protease patterns may lead to a more individualized characterization of the invasive potential of a tumour.

Of the genetic parameters, there is a high probability that c-*erb*B-2 will become a further new prognostic factor in gastric cancer. There is also evidence that the growth factor receptor *cripto* and the tumour suppressor p53 may be shown as new prognostic factors in future studies. Of the tumour-associated proteases besides the uPA system, evidence has accumulated for cathepsin D as a probable

Table 2 Status of current variables as prognostic factors in gastric cancer

	Established risk factor	High (or good) probability of becoming relevant	Potential relevance, yet to be tested	No relevance or low probability of becoming relevant
Established prognostic variables				
Patient-related			Age Sex	Pattern/duration of symptoms, weight loss, co-morbidity, immune status
Treatment-related	Surgical curability Quality of curative resection Hospital level		Allogeneic or autologous blood transfusion Adjuvant chemotherapy (FAMTX, EAP) Neoadjuvant chemotherapy Chemotherapy in non-resectable cancers (FAMTX, EAP, ELF)	Adjuvant chemotherapy (5-FU, FAM) Adjuvant radiation therapy Intraoperative radiation therapy
Tumour-related	pTNM Tumour localization		Grading (G) Lymphangiosis carcinomatosa Blood vessel infiltration	Laurén, Ming WHO classification Borrmann
Tumour markers in serum		Combination of CA 72-4 and CEA	CEA, CA 19-9, CA 72-4 CA 125, Sialyl Tn antigen ST-439, AFP	
New functional biological variables				
Tumour-associated proteases/protease inhibitors	uPA system (PAI-1)	(Cathepsin D)	MMPs, MT-MMP TIMPs Cathepsins B, E, G	α_2-Antiplasmin Plasminogen Antithrombin III
		(MMP-2 in combination with activating factors or in balance with TIMP-2)	α_2-Macroglobulin α_2-Macroglobulin receptor α_1-Antichymotrypsin α_1-Antitrypsin, protease patterns Other proteases like interleukin-1 converting enzyme)[81] (not discussed in this review)	tPA
Adhesion molecules		(CD44/CD44 splice variants) (E-cadherin)	ICAM, VLA-4, E-selectin	
Molecular parameters		c-*erb*B-2/p185	c-*met* (HGF receptor) c-*ras* EGF and EGF/TGF-α receptor	
		(p53) (*cripto*)	*pic1*, *MTS1* (p16) G1 and G2 cyclins Cyclin-dependent kinases *nm23*, *APC* *bcl-2* Genetic instability	
Minimal residual disease		Follow-up course of disseminated tumour cells in bone marrow (CK18 positive), uPA-R expression of disseminated tumour cells	Further phenotypic characteristics of disseminated tumour cells Perioperative evidence of disseminated tumour cells in bone marrow	

5-FU, 5-fluorouracil, FAM, fluorouracil adriamycin methotrexate; FAMTX, methotrexate, 5-FU and adriamycin; EAP, adriamycin, cisplatin and etoposide; ELF, etoposide, leucovorin and 5-FU; TNM, tumour node metastasis; WHO, World Health Organization, CEA, carcinoembryonic antigen; AFP, α-fetoprotein; uPA, urokinase-type plasminogen activator; PAI, plasminogen activator inhibitor; MMP, matrix metalloproteinase; MT-MMP, membrane-type matrix metalloproteinase; TIMP, tissue inhibitor of metalloproteinases; tPA, tissue-type plasminogen activator; ICAM, intercellular adhesion molecule; VLA, very late antigen; HGF, hepatocyte growth factor; EGF, epidermal growth factor, TGF, transforming growth factor; CK, cytokeratin; uPA-R, urokinase-type plasminogen activator receptor

prognostic factor. To a lesser extent MMP-2, in combination with activating factors or in balance with TIMP-2, may be shown as a prognostic factor in the future. Of the adhesion molecules, there is the possibility that E-cadherin and CD44 splice variants will become new prognostic factors. In addition, individual follow-up and phenotyping of disseminated tumour cells in bone marrow is a promising new approach to prognosis and tumour biology. An overview on the current status of prognostic factors in gastric cancer is shown in *Table 2*.

Benefits for the patient with gastric cancer can at present be obtained in establishing more detailed risk profiles, orientated at the specific functional properties of the tumour. By biological grading, new patient groups can be defined which should enable more precise planning of adjuvant treatment. However, increasingly attempts are being made to use these biological factors as new targets for anti-invasive and antimetastatic cancer therapy[208-212]. This has already resulted in the first clinical attempts to affect the uPA system (especially uPA-R) and the MMPs by synthetic inhibitors. Potentially, these and further ongoing approaches will lead to therapeutic inhibition of the proteolytic and thus the invasive potential of human cancer.

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Enteral nutrition is superior to parenteral nutrition in severe acute pancreatitis: results of a randomized prospective trial

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Background Parenteral nutrition is well established for providing nutritional support in acute pancreatitis while avoiding pancreatic stimulation. However, it is associated with complications and high cost. Benefits of enteral feeding in other disease states prompted a comparison of early enteral feeding with total parenteral nutrition in this clinical setting.

Methods Thirty-eight patients with acute severe pancreatitis were randomized into two groups. The first ($n = 18$) received enteral nutrition through a nasoenteric tube with a semi-elemental diet, while the second group ($n = 20$) received parenteral nutrition through a central venous catheter. Safety was assessed by clinical course of disease, laboratory findings and incidence of complications. Efficacy was determined by nitrogen balance. The cost of nutritional support was calculated.

Results Enteral feeding was well tolerated without adverse effects on the course of the disease. Patients who received enteral feeding experienced fewer total complications ($P < 0{\cdot}05$) and were at lower risk of developing septic complications ($P < 0{\cdot}01$) than those receiving parenteral nutrition. The cost of nutritional support was three times higher in patients who received parenteral nutrition.

Conclusion This study suggests that early enteral nutrition should be used preferentially in patients with severe acute pancreatitis.

Severe acute pancreatitis is accompanied by increased resting energy requirements and loss of protein mass resulting from the inflammatory response following necrosis or inflammation of the pancreas and retroperitoneal tissues[1]. This, combined with the absence of oral intake, leads to a persistently negative nitrogen balance that appears to be associated with a higher mortality rate as a result of the loss of function and structural integrity of vital organs[2–4]. Thus, the provision of early aggressive nutritional support is of utmost importance in this clinical setting.

Total parenteral nutrition (TPN) has been the standard practice for providing exogenous nutrients to patients with acute pancreatitis in order to improve nutritional status and at the same time to avoid pancreatic stimulation[5–8] However, TPN is associated with certain disadvantages. In particular, there is an increased risk of central catheter infection, severe hyperglycaemia, and other metabolic and electrolyte disturbances[5–8]. TPN may also promote gut barrier alterations due to increased intestinal permeability[9,10].

The use of early enteral feeding (EF) for nutritional support in patients with acute pancreatitis has not been evaluated systematically. The commonly encountered problems of gastric atony and outlet obstruction have limited the successful delivery of enteral formulas to patients with severe acute pancreatitis. However, these problems may be overcome if enteral nutrition were to be delivered to the small intestine distal to the ligament of Treitz using elemental or semi-elemental low-fat diets[2,11,12].

The efficacy, tolerance, clinical outcome and cost of EF and TPN have been evaluated in patients with severe acute pancreatitis.

Patients and methods

Between July 1990 and December 1995, 326 patients with acute pancreatitis were treated in this unit. Some 40 consecutive patients with severe necrotizing pancreatitis admitted during this period were studied. The study was designed in accordance with the principles of the declaration of Helsinki and was approved by the local hospital committee. Informed consent was obtained from all participating patients or from the next of kin if patients were unable to respond for themselves.

Inclusion criteria

Inclusion criteria for randomization were the presence of three or more criteria according to the Imrie classification[13] or Acute Physiology And Chronic Health Evaluation (APACHE) II score[14] of 8 or more, C-reactive protein concentration greater than 120 mg/l within 48 h of admission, and grade D or E by computed tomography (CT) according to the Balthazar criteria[15]. Patients who were treated elsewhere for more than 2 days before admission to this hospital were not included.

Conservative treatment

All patients required intensive monitoring for more than 72 h During the acute phase, treatment consisted of adequate fluid replacement through a central venous catheter with haemodynamic monitoring and assistance of respiratory or renal function when needed. Analgesics were given as required to all patients, and an H_2 blocker was given to prevent stress ulcers. A nasogastric tube was inserted as needed to keep the stomach empty. Prophylactic use of imipenem was started on admission and continued until clinical recovery and restoration of normal C-reactive protein concentrations. Other antibiotics were used as required to manage proven infection. The choice of antibiotic depended on the type of infection and was based on bacterial cultures when available.

Monitoring

C-reactive protein was measured three times per week following admission, and blood cultures were performed at least twice a

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week and immediately on clinical suspicion of sepsis. Bacteriological culture of urine samples was performed twice a week. Central venous lines were changed every 7 days or earlier if the line was thought to be the cause of unexplained fever. The tips of all removed lines were cultured Gram staining and bacterial cultures were also obtained weekly from CT-guided biopsy samples of pancreatic or peripancreatic tissue or fluid from patients suspected to have infected necrosis because of persistent fever, rise in C-reactive protein concentration, or fluid collections detected by contrast-enhanced CT[16]. Blood culture-positive sepsis, pneumonia and/or adult respiratory distress syndrome, urinary infections, and infected necrosis or intra-abdominal abscess were recorded as infectious complications. Diarrhoea was defined as unformed water stool occurring three or more times during a 24-h period.

Operative treatment

A decision to operate was based on the following clinical criteria: development of an acute abdomen requiring immediate surgery, verified infected necrosis, persistent or increasing organ dysfunction despite maximum intensive care for at least 5 days. The standard procedures were debridement of devitalized tissue with preservation of vital pancreatic tissue using the open drainage technique and, in some cases, local postoperative lavage[17].

Randomization and nutritional methods

Patients were assigned on admission to one of two treatment groups by means of numbered envelopes. In the EF group, a nasoenteric feeding tube (Flexiflo 10 Fr, 115 cm; Ross Lab, Columbus, Ohio, USA) was placed fluoroscopically distal to the ligament of Treitz by experienced radiologists within the first 48 h after admission. This procedure was unsuccessful in two patients who were then excluded from the study. EF began immediately after patients returned to the intensive care unit (ICU), provided that they were well resuscitated and stable. Feeding began with a peptide-based formula (Reabilan HN; Roussel ulcef Nutrition, Montpellier, France). Reabilan HN has a caloric density of 1 33 kcal/ml and provides 58 g protein, 158 g carbohydrate and 52 g fat (61 per cent long-chain triglycerides, 39 per cent medium-chain triglycerides) per litre, with a non-protein kcal per g nitrogen ratio of 125:1 and osmolality 490 mosm/kg. Full-strength formula was started at 25 ml/h and advanced by 25 ml/h every 4 h, until the patient's target rate was reached

In the TPN group the parenteral feed contained crystalline L-amino acids (Vamin 18FE; Kabi Pharmacia, Stockholm, Sweden), carbohydrate in the form of dextrose, fat emulsion (Lipofudin long-chain/medium-chain triglycerides 20 per cent; Braun, Melsungen, Germany), vitamins and minerals. The all-in-one system was used and was administered by continuous 24-h infusion. All patients received TPN through the subclavian polyurethane catheter TPN was infused initially at a rate of 40 ml/h and was advanced by 20 ml/h every 4 h until patient's target rate was reached. The target rate in both groups was to provide 1·5–2 g protein per kg per day and 30–35 kcal per kg per day The non-protein calorie:nitrogen ratio was 100–125:1.

In patients requiring surgery during the course of the disease, artificial nutrition was discontinued 6 h before surgery, and was restarted during the first 24 h following surgery. In patients receiving EF the feeding tube was manipulated through the pylorus and placed within the first 25 cm of the jejunum at the end of surgery. Correct positioning of the tube was verified by radiological assessment once the patient had returned to the ICU.

Nutritional support monitoring

Insulin was administered to maintain blood glucose levels below 200 mg/dl. Serum electrolytes, total protein, albumin, serum amylase, triacylglycerols and cholesterol were measured and liver function tests were carried out daily by routine hospital methods until biochemical stability was achieved, and twice a week thereafter. The success of nutritional support was determined by nitrogen balance which was calculated by subtracting nitrogen losses (total urinary nitrogen excreted over 24 h) plus an estimated stool and obligatory nitrogen loss of 2 g from the total nitrogen administered during that 24-h period. Total urinary nitrogen was analysed using a pyrochemiluminescent system (Antek Instruments, Houston, Texas, USA) Nitrogen balance was calculated before the onset of artificial nutrition support and once a week during the course of the study.

Outcome measurements

At the time of hospital discharge, patient records were reviewed for confirmation of complications during the course of the disease and classified as: (1) those related to artificial nutritional support, (2) those due to acute pancreatitis and (3) those due to other septic complications. The length of ICU stay, length of hospital stay, number of days on artificial ventilation, number of days receiving tube feedings or TPN, number of antibiotics and number of days on antibiotics were recorded. The mean cost of EF and TPN per day was also calculated.

Statistical methods

Statistical analysis was by the χ^2 test for discrete variables, by the unpaired Student's t test for parametric analysis and by the Kruskal–Wallis test for non-parametric analysis; $P \leq 0{\cdot}05$ was considered statistically significant.

Results

Comparison of patient groups

The groups were comparable as demonstrated in *Table 1*. The severity of pancreatitis was also compared by CT. According to the Balthazar criteria[15], 11 patients were classified as grade D (four from the EF group and seven from the TPN group) and 27 patients as grade E (14 from the EF group and 13 from the TPN group). Contrast-enhanced CT showed 30 per cent necrosis (low enhancement less than 30 Housfield units) of the pancreas in 11 patients (four from the EF group and seven from the TPN group), 30–50 per cent necrosis in 22 patients (12 from the EF group and ten from the PN group) and more than 50 per cent necrosis in five patients (two from the EF group and three from the TPN group).

Tolerance and nutritional data

Both enteral and parenteral nutrition were well tolerated, and no patient developed clinical symptoms or laboratory abnormalities as a result of an adverse effect on the course of the disease. As shown in *Table 2* there were no statistically significant differences between the two groups with regard to ICU support, use of antibiotics or hospital stay. The total number of days during which patients were on artificial nutritional support was similar in both groups (mean 34·8 days in the EF group and 32·8 days in the TPN group). Protein intake (1·43 *versus* 1·45 g per kg per day respectively) and non-protein caloric intake (24·1 *versus* 24·5 kcal per kg per day) were also comparable between groups. There were no significant differences in nitrogen balance between the two groups during the course of the study. In both groups nitrogen balance improved progressively with the duration of artificial nutrition support (*Fig. 1*).

Morbidity

Artificial nutrition-related complications. There was no occlusion of the jejunal feeding tubes or any mechanical

Table 1 Patient groups

	Enteral feeding (*n* = 18)	Total parenteral nutrition (*n* = 20)
Demography		
Sex ratio (M:F)	8:10	7:13
Mean(s.d.) (range) age (years)	63·0(10·7) (23–70)	67·2(8·9) (31–72)
Aetiology and duration of pancreatitis		
Cholelithiasis	14	16
Alcohol	3	2
Other	1	2
Mean(s.d.) duration of symptoms (days)	1·7(1·3)	1·8(1·5)
Prognostic signs		
Mean(s.d.) (range) positive Imrie criteria*	4·2(0·9) (3–5)	4·6(1·1) (3–6)
Mean(s.d.) (range) APACHE II score†	12·7(2·6) (8–15)	11·8(1·9) (8–15)
Mean (range) maximum C-reactive protein level in first 48 h (mg/l)‡	290 (157–420)	335 (140–513)

*Imrie criteria[13] were available for 16 patients in the enteral feeding (EF) group and 19 in the total parenteral nutrition (TPN) group. †Acute Physiology And Chronic Health Evaluation (APACHE) II scores[14] were available for seven patients in the EF group and six who had TPN. ‡Based on 15 patients in the EF group and 17 in the TPN group

Table 2 Conservative treatment and hospital stay

	Enteral feeding (*n* = 18)	Total parenteral nutrition (*n* = 20)
Mean (range) intensive care unit stay (days)	11 (5–21)	12 (5–24)
Mean (range) time on ventilator (days)*	15 (6–16)	11 (7–31)
Mean (range) haemodialysis time (days)†	14 (12–16)	15 (11–19)
Mean(s.d.) no. of antibiotics	1·7(0·9)	2·0(0·9)
Mean(s.d.) time on antibiotics (days)	22(6)	23(6)
Mean (range) hospital stay (days)	40 (25–83)	39 (22–73)

*Five patients in the enteral feeding (EF) group and seven who had total parenteral nutrition (TPN). †Two and three patients in EF and TPN groups respectively

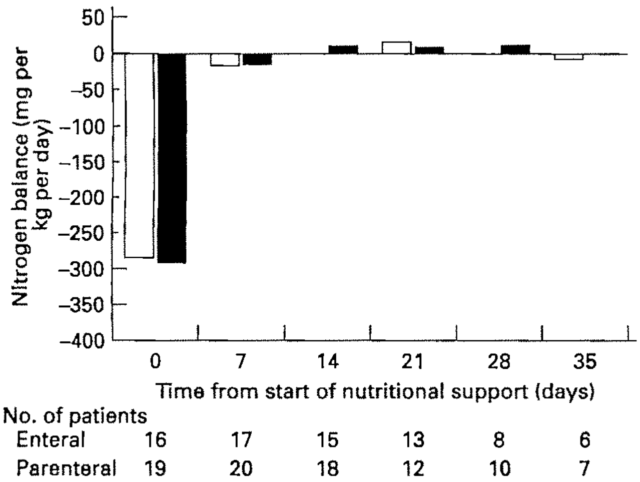

Fig. 1 Nitrogen balance in patients with acute pancreatitis who had enteral (☐) or total parenteral (■) nutritional support

complication leading to premature termination of the study in any patient. Diarrhoea developed in three patients from the TPN group and in six from the EF group. No complications occurred during placement of the central catheters in either group. Two patients from the TPN group developed catheter-related sepsis which was attributed to *Staphylococcus epidermidis* (*Table 3*). Hyperglycaemia was the most frequent metabolic complication during the administration of nutritional support, occurring in 14 patients from the EF group and 18 who had TPN. Severe hyperglycaemia (blood glucose level above 200 mg/dl), which required administration of crystalline insulin, was twice as frequent in patients fed parenterally than in those fed enterally (*Table 3*). There were no additional major metabolic complications in either group.

Pancreatitis-related complications. Complications directly related to the pancreatitis are shown in *Table 3*. In the EF group, two patients underwent operation, one of whom required a second operation. In the TPN group, four patients underwent surgery, all of whom required at least two operations for a total of 11 surgical procedures.

Non-pancreatitis-related complications. Complications not related to the pancreatitis are also shown in *Table 3*. The EF group had significantly less morbidity than the TPN group ($P < 0·05$) and developed fewer septic complications. The mean number of infections per patient was also significantly lower in patients receiving EF than in those receiving TPN (0·56 *versus* 1·35, $P < 0·01$); however, when these infections were analysed separately the differences were not significant (*Table 3*). These results show that when, for whatever reason, it becomes necessary to administer TPN instead of EF, the risk of developing complications is 3·47 times higher than it would be if EF could be implemented successfully (odds ratio 3·75 (95 per cent confidence interval 0·95–14·7)).

Mortality rate

Three of the 38 patients died, one in the EF group and two in the TPN group. The cause of death in all cases was sepsis and multiorgan failure.

Table 3 Patient morbidity

	Enteral feeding ($n = 18$)	Total parenteral nutrition ($n = 20$)
Artificial nutrition-related complications		
No. of patients with catheter-related sepsis	0	2
No. of patients with hyperglycaemia > 200 mg/dl	4	9
Pancreatitis-related complications		
No. of patients with infected pancreatic or peripancreatic necrosis	1	4
No of patients with abscess formation	1	0
No. of patients with acute pseudocysts	0	1
No of patients with pancreatic fistula	0	2
Non-pancreatitis-related complications		
Blood culture-positive sepsis	1	3
Urinary tract infection	1	2
Pneumonia/ARDS	2	4
Total no of patients with septic complications	5 (6)	10* (15)
Total no. of patients with any complication	8 (10)	15† (27)

Values in parentheses are total number of complications. ARDS, adult respiratory distress syndrome $^*P < 0{\cdot}01$, $^\dagger P < 0{\cdot}05$ (Kruskal–Wallis test)

Cost

The cost of TPN at this institution for this patient group was approximately £100 per patient per day. In comparison, the cost of EF using the commercially prepared semi-elemental diet was about £30 per patient per day; this means a daily cost saving of about £70 when EF is used instead of TPN. When the potential increase in cost due to the increased rate of complications associated with TPN is taken into account, this cost difference becomes even greater.

Discussion

The aim of this study was to determine if nutritional status could be maintained equally by the enteral and parenteral routes in patients with severe acute pancreatitis. Secondary points of interest included the rate of complications and financial cost of treatment. The results showed clearly that early EF was well tolerated following acute severe pancreatitis and was of comparable efficacy to TPN. Moreover, EF was accompanied by significantly fewer complications and was much lower in cost than TPN.

Nutritional status can deteriorate rapidly in patients with severe acute pancreatitis[1,4], and early nutritional support is important to ensure optimum recovery[5]. Feeding should therefore be initiated as soon as possible and be continued until adequate oral intake is achieved.

In recent years several retrospective and non-randomized prospective trials have looked into the efficacy of parenteral nutrition in acute pancreatitis of varying disease severity[4–8]. From these studies it appears that the main benefit of TPN in patients with severe acute pancreatitis is the improvement of nutritional parameters and the maintenance of lean body mass resulting in a decrease in mortality and morbidity rates[4,5]. TPN does not, however, seem to affect the progress of pancreatic inflammation[4–8,12]. Furthermore, TPN is accompanied by a potential increase in catheter-related sepsis[5,6,8], and a possible exacerbation of metabolic disturbances, in particular hyperglycaemia[5,8]. Finally, the administration of TPN is very costly[18]. All of these findings have been confirmed in the present study.

On the other hand, the use of early enteral nutritional support during the treatment of acute severe pancreatitis has not been evaluated to date. Gastric and intraduodenal infusions using either elemental diets or intact nutrients stimulate pancreaticobiliary secretion by several pathways[19] and therefore should be avoided owing to potential exacerbation of the pancreatic inflammatory process[2,11]. It has also been shown that the infusion of elemental or semi-elemental low-fat diets beyond the ligament of Treitz produces some hormone stimulation[11,19] and pancreatic response[20–22], but the pancreatic fluid secreted is watery and low in enzyme concentration. Furthermore, in patients with chronic pancreatitis, it has been shown that, although both EF and parenteral feeding stimulate secretion, the volume of secretion and the content of bicarbonate and enzymes are similar, regardless of the feeding method[23]. These findings led the authors to conclude that jejunal delivery of appropriate substrates would involve minimal pancreatic secretion.

Successful and safe jejunostomy feeding has been reported in patients requiring laparotomy during the course of severe pancreatitis[2,11,17]. Kudsk *et al.*[24] placed feeding jejunostomies in 11 patients undergoing laparotomy for septic or haemorrhagic complications of severe acute pancreatitis. Five of these patients were operated within 48 h of the onset of pancreatitis and were fed immediately after surgery with an elemental diet with no adverse effect on the clinical course of the disease. Several clinicians advocate the placement of a feeding jejunostomy in all patients who undergo surgery for pancreatitis[2,11,17,24]. On the other hand, the use of jejunostomies can lead to major complications[2,25,26].

In this study there was a 90 per cent rate in the placement of nasojejunal tubes without complication. Furthermore, the administration of a semi-elemental diet low in long-chain triglycerides was shown to be completely safe and without adverse effects on the clinical course of the pancreatitis. Finally, it was shown that the administration of early EF under these conditions is equally as effective as TPN in maintaining patient lean body mass and nutritional status. EF in this study was also associated with fewer infections but this difference was not statistically significant probably because of the small number of patients in the study. On the other hand, there were significantly fewer total complications than with TPN. A similar reduction in septic complications has also been observed in other clinical situations including severe trauma and burns[26,27]. Although the exact mechanism of this reduction is unknown, experimental and clinical data[9,28] indicate that early enteral nutrition is capable of maintaining the integrity and function of the intestinal mucosa. On the contrary, the administration of TPN may lead to malfunction of the intestinal mucosal barrier which may promote gut origin sepsis[29]. The cause of septic complications in the EF and TPN groups in the present study was multifactorial, and it can only be speculated that EF improves the gut immune system, restores normal gut structure and microflora, and aids the mucosa in withstanding challenges to these systems. It is, in fact, still unclear whether EF improves the rate of septic morbidity or whether TPN itself causes an increase in septic complications.

The only major metabolic complication encountered was hyperglycaemia. In patients receiving EF the frequency of severe hyperglycaemia was much less than for patients on TPN as was the quantity of insulin required to achieve satisfactory regulation of blood glucose. Since caloric intake was similar in both groups, it is assumed that the better glycaemic control in patients fed enterally can be attributed to more physiological secretion of biochemical mediators in the gut and liver during EF[30].

In conclusion, the results of this prospective randomized study suggest that the enteral route should be used preferably for nutritional support in patients with acute severe pancreatitis.

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Gastric intramucosal pH predicts death in severe acute pancreatitis

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Background This study tested the hypothesis that gastric intramucosal pH (pHi) can predict death in severe acute pancreatitis.

Methods Seventeen consecutive patients with predicted severe acute pancreatitis were studied prospectively. Four died from complications related to pancreatitis. Gastric pHi was measured by nasogastric tonometry at least every 12 h for the first 48 h after admission and then on a daily basis during the first week.

Results The lowest pHi recorded during the first 48 h was significantly less in those admitted to the intensive care unit than that in those who remained on the surgical ward ($P = 0{\cdot}0015$) and in non-survivors compared with the survivors ($P = 0{\cdot}009$). A receiver-operator characteristic curve defined a pHi of 7·25 as the optimal cut-off point to predict death (sensitivity 100 per cent, specificity 77 per cent, overall predictive value 82 per cent).

Conclusion These results suggest that splanchnic ischaemia may be an important determinant of outcome in patients with severe acute pancreatitis.

The mortality rate associated with severe acute pancreatitis remains high[1] and any further improvement in outcome will only occur when the pathogenesis of acute pancreatitis is better defined and is used to develop specific interventions.

There is evidence to suggest that ischaemia–reperfusion injury with its associated oxidative stress plays a major role in the pathogenesis of acute pancreatitis[2–4]. The susceptibility of the pancreas to ischaemic injury has been demonstrated in both experimental and clinical studies[5–9]. Patients with pancreatitis often have clinical signs of hypovolaemia at the time of admission, resulting from a significant retroperitoneal 'third space' loss of fluid. Because the splanchnic vasoconstriction that occurs in response to this hypovolaemia may persist despite seemingly adequate resuscitation[10,11], it is not unreasonable to suggest that the pancreas may be subject to continuing ischaemic injury.

An indirect measure of splanchnic ischaemia is now possible with nasogastric tonometry[12,13]. Anaerobic metabolism within the gastric mucosal cells results in a low intramucosal pH (pHi); the indirect measurement of this via tonometry has been validated in low-flow states[14,15] and has been shown to be reliably and linearly related to indices of splanchnic tissue oxygenation as measured in the hepatic vein[16]. In clinical studies of patients with severe sepsis and critical illness, pHi has been shown to predict outcome[17–20].

The aim of this study was to test the hypothesis that pHi predicts death in patients with severe acute pancreatitis.

Patients and methods

All patients admitted with predicted severe acute pancreatitis were considered eligible for this study if their clinical team wished them to have a nasogastric tube inserted. This study was approved by the Northern Regional Health Authority Ethics Committee and informed consent was obtained from each patient or a relative. The diagnosis of acute pancreatitis was based on the presence of appropriate clinical or radiological evidence accompanied by a serum amylase concentration greater than 1000 units/l (Phadebas; Pharmacia Diagnostics, Uppsala, Sweden; normal range 70–300 units/l) The severity of pancreatitis was predicted using the modified Glasgow score[21] where three or more positive criteria represents severe disease. All patients proved to have severe pancreatitis based on the Atlanta classification[22]. The severity of pancreatitis was also assessed on a daily basis by calculation of an Acute Physiology And Chronic Health Evaluation (APACHE) II score[23]

A nasogastric tonometer (TRIP NGS Catheter, Tonometrics, Worcester, Massachusetts, USA) was used to measure the gastric pHi at least every 12 h for the first 48 h of admission and then on a daily basis during the first week. Saline was instilled into the carbon dioxide permeable balloon on the tonometer and allowed to equilibrate for 60–90 min. The saline was then withdrawn anaerobically and analysed for carbon dioxide by a blood gas analyser (IL1312, Instrumentation Laboratory Company, Lexington, Massachusetts, USA). At the same time blood from the radial artery was taken to measure bicarbonate, arterial pH, carbon dioxide and base excess. The gastric pHi was calculated using a modified Henderson–Hasselbalch formula, taking the actual arterial bicarbonate concentration and the steady-state adjusted carbon dioxide tension of the tonometer sample. H_2-receptor blockers were not administered routinely.

Markers of the systemic inflammatory response used in this study were serum C-reactive protein (CRP) level and total white blood cell count

Statistical analysis was performed using Fisher's exact test for categorical data and the Mann–Whitney *U* test for continuous and ordinal data. Because of the small number of patients, data are presented as median (range). $P < 0{\cdot}05$ was accepted as significant.

Results

Seventeen consecutive patients (ten men and seven women, of median age 63 (range 27–83) years) with predicted severe pancreatitis were studied. The overall mortality rate was four of 17 and the patients were divided into two groups: survivors ($n = 13$) and non-

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survivors ($n = 4$). Two of the patients died early (on days 2 and 3 after admission) with respiratory failure and the other two died late (days 40 and 72) with multiple organ failure. Seven of the 13 survivors and three of four non-survivors were admitted to the intensive care unit.

There was no significant difference between the two groups in the aetiology of pancreatitis, the duration of symptoms before admission and the severity of pancreatitis (APACHE II) at the time of recruitment or within 48 h of recruitment (*Table 1*). The survivors had a significantly lower predicted severity score (modified Glasgow) than the non-survivors ($Z = -2·36$, $P = 0·02$). Pancreatic necrosis was diagnosed in six of the 12 survivors and two of the three non-survivors who underwent contrast-enhanced computed tomography at some stage during their hospital stay.

There was no significant difference between the two groups in markers of the systemic inflammatory response at the time that tonometry was performed: CRP ($Z = -0·39$, $P = 0·70$) and white blood cell count ($Z = -0·07$, $P = 0·95$) (*Table 2*). However, the tonometry results were significantly different between the patient groups. Patients admitted to the intensive care unit had a significantly lower pHi within the first 48 h of recruitment (median 7·24 (range 7·01–7·36)) than those who remained on the surgical ward (median 7·37 (range 7·24–7·46)) ($Z = -2·44$, $P = 0·015$). The non-survivors had a significantly lower pHi within the first 48 h of recruitment ($Z = -2·60$, $P = 0·009$) and within the first week ($Z = -2·04$, $P = 0·04$) than those who survived. This gastric intramucosal acidosis was not matched by a corresponding significant difference in systemic (arterial) acidosis ($Z = -1·36$, $P = 0·17$) or base excess ($Z = -0·40$, $P = 0·69$) (*Table 2*).

Further evidence for the importance of pHi in predicting clinical outcome was demonstrated by the significant negative correlation ($r = -0·6$, $P = 0·03$, linear regression) between overall hospital stay and the lowest pHi for the surviving patients ($n = 13$) (*Fig. 1*).

A receiver–operator characteristic curve was constructed to define the optimal cut-off point for pHi in predicting death (*Fig. 2*). A cut-off value for pHi of 7·25 yielded a sensitivity of 100 per cent, specificity 77 per cent and overall predictive value for death of 82 per cent (*Fig. 3*). The same cut-off value of pHi less than 7·25 predicted the need for intensive care with a sensitivity of 60 per cent, specificity 86 per cent and overall predictive value 71 per cent.

Discussion

This study demonstrates that gastric pHi predicts death in patients with severe acute pancreatitis, and to a lesser extent the need for intensive care support. This ability to predict outcome is not just because pHi is a reflection of systemic acidosis or overall physiological status.

The profound inflammatory response associated with acute oedematous pancreatitis results in a significant retroperitoneal 'third space' loss of fluid. The homoeostatic

Table 1 Patient details, duration of symptoms before recruitment, and aetiology and severity of pancreatitis

	Survivors ($n = 13$)	Non-survivors ($n = 4$)	Z‡	P
Age (years)*	57 (27–83)	72 (45–79)	−0·79	0·43
Sex ratio (M:F)	8:5	2:2		0·99§
Aetiology of pancreatitis				0·58¶
Gallstones	6	3		
Alcohol	1	1		
After ERCP	2	0		
Other	4	0		
Duration of symptoms (h)*	30 (10–336)	25 (17–670)	−0·34	0·73
Predicted severity of pancreatitis*†	5 (3–6)	6 (4–7)	−2·36	0·02
Severity of pancreatitis (APACHE II score)				
At the time of recruitment	11 (3–17)	12 (8–19)	−0·43	0·67
Within 48 h of recruitment	12 (8–17)	15 (8–19)	−0·46	0·46

*Values are median (range). †Number of modified Glasgow criteria. ERCP, endoscopic retrograde pancreatography; APACHE, Acute Physiology and Chronic Health Evaluation. ‡Mann–Whitney U test; §Fisher's exact test; ¶Fisher's exact test between gallstones and all other causes combined

Table 2 Markers of sepsis, arterial pH and base excess, and tonometry data for survivors and non-survivors with severe acute pancreatitis

	Survivors ($n = 13$)	Non-survivors ($n = 4$)	Z*	P
Markers of sepsis				
C-reactive protein (mg/l)	241 (87–559)	274 (75–336)	−0·39	0·70
White cell count ($\times 10^9$ per l)	17·7 (6·9–34·1)	20·3 (16·3–24·0)	−0·07	0·95
Arterial blood gas results				
Arterial pH	7·36 (7·32–7·43)	7·32 (7·19–7·43)	−1·36	0·17
Base excess	−3·0 (−11·0 to 2·0)	−3·1 (−5·3 to −1·0)	−0·40	0·69
Tonometry				
Lowest pHi (within first 48 h)	7·31 (7·18–7·46)	7·19 (7·01–7·24)	−2·60	0·009
Lowest pHi (within first week)	7·25 (7·08–7·42)	7·14 (7·01–7·24)	−2·04	0·04

Values are median (range). pHi, intramucosal pH *Mann–Whitney U test

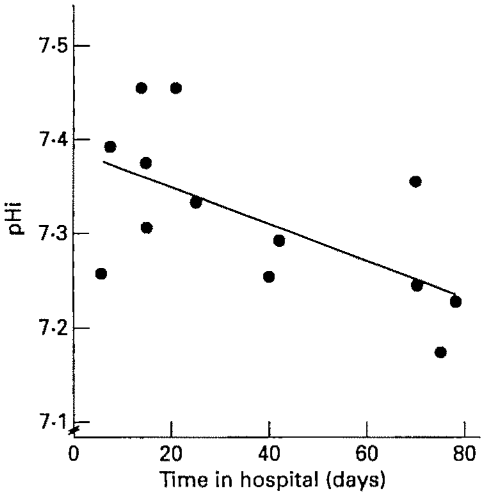

Fig. 1 Intramucosal pH (pHi) (lowest value within the first 48 h) plotted against length of hospital stay for surviving patients ($n = 13$) $r = -0.60$, $F = 6.26$, $P = 0.03$ (linear regression)

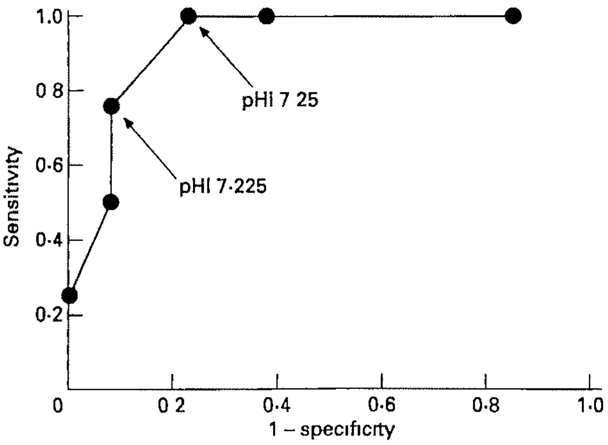

Fig. 2 Receiver–operator characteristic curve used to determine the optimal intramucosal pH (pHi) with which to predict death

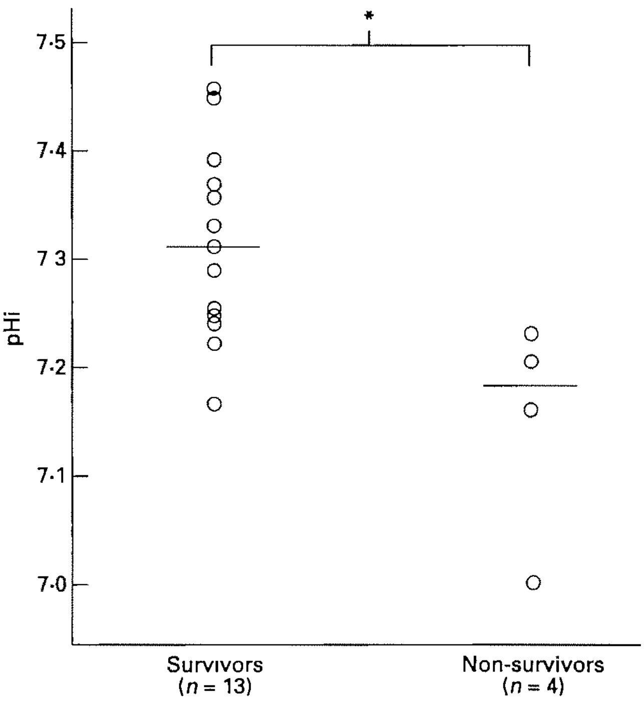

Fig. 3 Lowest intramucosal pH (pHi) in the first 48 h in survivors and non-survivors. Horizontal bars represent median values. $^*Z = 2.6$, $P = 0.009$ (Mann–Whitney U test)

response to this hypovolaemia includes splanchnic vasoconstriction[12]. The splanchnic organs of patients who appear to be adequately resuscitated, without persisting clinical evidence of hypovolaemia, may continue to suffer from splanchnic ischaemia[10]. The experimental findings in acute pancreatitis of increased capillary permeability within the pancreas[24], clinical evidence of neutrophil activation[25,26], and the appearance of pancreatic tissue hypoperfusion in the early stages of the disease on contrast-enhanced computed tomography[27], are in keeping with ischaemia–reperfusion as a mechanism for local pancreatic injury and the associated systemic effects. Further support for this mechanism in the pathogenesis of acute pancreatitis has come from recent work[28] which showed that serum manganese superoxide dismutase, a key antioxidant enzyme and a marker of ischaemia–reperfusion injury in myocardial infarction[29], was significantly raised in patients with severe compared with mild pancreatitis. This increase was correlated with peripheral serum markers of lipid peroxidation (malondialdehyde) and neutrophil activation (myeloperoxidase) and was associated with decreased serum ascorbic acid levels (an important antioxidant)[28].

This study does not provide direct evidence to suggest that the adverse outcome predicted by tonometry is driven primarily by injury to the pancreas. Ischaemia–reperfusion injury of the small bowel, with subsequent failure of the gut barrier, may well be the culprit[12].

Nasogastric tonometry is a relatively non-invasive method for determining the degree of splanchnic mucosal ischaemia which, although not previously used to investigate patients with acute pancreatitis, has been used in studies of critically ill patients to demonstrate that death (and multiple organ failure) is more closely related to a low pHi than APACHE II[17,18], arterial pH, mixed venous pH, lactic acid and oxygen delivery and consumption[19,20,30]. There is some controversy over whether the measurement of base excess is as useful as pHi in predicting death[13,31]. Chang *et al.*[30] found that base excess was a better predictor of death than pHi in critically ill patients with trauma but admitted that this might be due to selection bias as all patients had raised base deficit or lactate value at the time of recruitment. The present study, in which there was no difference in base excess between survivors and non-survivors, demonstrates that pHi is a better predictor of death than base excess, and this is in keeping with other studies[17,20]. Gutierrez *et al.*[17] have shown that non-survivors of critical illness have a significant reduction in mixed venous pH, but to a lesser extent than the reduction in pHi. Taken together, these studies suggest that the impairment of splanchnic mucosal perfusion is important in determining the outcome of patients with critical illness.

There is no agreement in the literature about which cut-off value for pHi best predicts clinical outcome. Some studies have suggested that a pHi lower than 7·35 or 7·3 is predictive[17,18,32,33], while Chang *et al.*[30] stated that 7·1 was the clinically significant cut-off value for pHi. The data from this study show that the cut-off value for pHi that best predicts death is 7·25, between these two extremes.

It might be argued that the failure to routinely use histamine receptor antagonists invalidates the results of this study[12]. Although reducing gastric acidity might make the results of this study more significant, the effect would be minor and there has been a move away from the use of this type of drug in intensive care patients because of the increased risk of nosocomial pneumonia[13,20,31].

Gastric tonometry has also been used to monitor the response to resuscitation. Doglio *et al.*[18] and Chang *et al.*[30] found that patients in whom resuscitation failed to correct a low gastric pHi on admission had a higher mortality rate than those in whom pHi returned to normal. Resuscitation guided by repeated measurement of pHi has been shown to improve survival in critically ill patients with normal pHi on admission, but not in patients with a low pHi[17]. These data have led to the concept that pHi might be a better endpoint of resuscitation than the commonly used haemodynamic parameters or predefined levels of oxygen delivery and consumption[32]. In uncompensated shock these parameters are useful, but once resuscitation is in progress pHi might be an important marker of the adequacy of resuscitation. Significant perioperative plasma volume expansion with colloid in patients who had undergone bypass cardiac surgery resulted in a raised gastric pHi and a significant reduction in hospital stay and the incidence of complications[34].

This study has demonstrated that nasogastric tonometry is a simple and effective way to predict clinical outcome in patients with severe acute pancreatitis, and can be used in the ward as well as in the intensive care unit.

Acknowledgements

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Surgical strategy for the management of hilar bile duct cancer

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Background Since the first attempts at resection of Klatskin tumours, an increasingly aggressive surgical treatment has been proposed. Results obtained after examination of the specimen have shown that a significant proportion of resections were palliative. Curative resection appears to be difficult to perform selectively.

Methods This retrospective study evaluates the results of a surgically-oriented management of hilar bile duct cancers. Thirty-nine patients were operated on in the period 1982–1994. Eighteen resections were carried out, requiring liver resection in 13 cases. Pathology of the specimen showed that the resection had been curative in 14 cases. The remaining 21 patients had surgical palliation, i.e. bypass and/or stenting.

Results In the resection group, there was no death but four patients suffered severe complications. The 1- and 5-year survival rates were 67 and 47 per cent respectively, with a median survival of 26 months. In the palliation group, the mortality rate was 14 per cent and median survival was 7 months.

Conclusion In the absence of evident contraindications, surgical exploration is worthwhile as it allows detection of the cases where curative resection is possible. Curative resection often requires a major hepatectomy, but mortality and morbidity may be kept low, and it offers a real hope of cure.

Since the description of adenocarcinoma of the upper third of the extrahepatic bile ducts by Klatskin[1], the therapeutic approach to this cancer has changed. After Longmire *et al.*[2] reported the first resection, a more aggressive surgical approach has been proposed[3,4]. Results obtained in many series[5,6] have shown that a significant proportion of the resections were found to be palliative, that is there was microscopic tumour invasion of the margins. Curative resection appeared to be difficult to perform selectively; surgical resection was considered as a treatment *per se* and its curative or non-curative status was a secondary finding discovered at the time of specimen examination. The survival reported after such an attitude, mixing patients with curative and palliative resections, was disappointing[5,6]. In this setting, minimal therapy with percutaneous placed stents[7] emerged, and more and more patients are now proposed for such therapy, maybe missing the opportunity of curative resection. Appropriate selection of patients for palliative stenting or curative surgical removal of the tumour is an unsolved question.

Since 1982 in the authors' department, the following approach has been adopted: in the absence of clear contraindication of resection (i.e. metastases, bilateral peripheral extension towards the intrahepatic bile ducts, or portal vein thrombosis) patients have undergone a surgical exploration with the aim of doing a radical resection. This radical resection was carried out if, and only if, after a lengthy exploration with repeated frozen-section examination, no metastasis and no regional extension was found and if a free margin of resection could be expected. If those conditions were not fulfilled, a palliative procedure (bypass and/or intubation) was carried out in the same operating session. The authors tried to avoid palliative resection and performed no extended procedures with vein resection or pancreatectomy.

This approach, with wide surgical indications for surgical exploration but restricted indication for resection, is evaluated in this paper. Thirty-nine patients operated on over a 12-year period are reviewed.

Patients and methods

Thirty-nine patients, 22 men and 17 women, of median age 62 (range 28–87) years were operated on in the period 1982–1994 for a cancer of the upper third of the extrahepatic bile ducts[8]. In the same study period, 11 patients received a non-surgical palliation, due to poor general condition making them unfit for major surgery ($n = 6$), peripheral bilateral intrahepatic extension ($n = 1$), or evidence of distant metastases ($n = 4$). Thus the patients selected for surgery formed 78 per cent of the total of 50 patients admitted in the surgical department during this period. Preoperative assessment included ultrasonography, Doppler sonography and preoperative percutaneous cholangiography at least. Preoperative percutaneous cholangiography was performed with a fine needle no more than 12 h before surgery, and no biliary drain was left in place. No preoperative treatment (e.g. biliary drainage or portal embolization) was performed.

The first step of the surgical exploration was to look for tumour spread outside the liver (peritoneal fluid, peritoneal seeding, coeliac lymph node). The hepatic artery and the portal vein were dissected. The type of resection to be performed was guided by preoperative imaging, especially transhepatic cholangiography. Evaluation of the tumoral extension continued during the surgical exploration. If a hepatic resection was planned, the pedicle of the part of the liver that was to be resected was not dissected, as vascular involvement limited to artery or portal vein on this side was not considered a contraindication for curative resection. The bile duct was exposed above the tumour and the site of the projected anastomosis was explored by dissection and palpation (more easily done on the left pedicule). The site of the proposed duct division was a minimum of 1 cm above the tumour, to enable a curative resection. Macroscopic evaluation was always associated with tissue sampling for frozen-section examination as soon as suspicious tissue was encountered. A frozen-section examination of the bile duct margins after resection was performed routinely.

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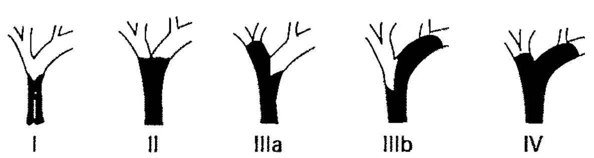


Fig. 1 Bismuth and Corlette classification of hilar bile duct tumours[5]. Type I: lesion of the main hepatic duct not involving the main confluence. Type II: lesion involving the confluence but clear of the right and left hepatic ducts. Type IIIa: lesion involving the right hepatic duct. Type IIIb: lesion involving the left hepatic duct. Type IV: lesion involving the right and left hepatic ducts

When resection was decided, it proceeded from the lowest accessible level of the bile duct upwards, *en bloc* with the cellulolymphatic tissue of the hepatic pedicle and the lymph nodes of the hepatic artery group, to achieve 1 cm macroscopic clearance above the upper limit of the tumour. The upper and lower margins of resection were examined on frozen sections. Liver resection was tailored to the stage of the tumour (Bismuth and Corlette classification[5]) (*Fig. 1*). Stage I and II tumours were simply excised. In stage III tumours a hepatectomy (left, right, or extended right) was performed on the side of the peripheral involvement. Stage I and II tumours with unilateral peripheral involvement of the blood vessels or the hepatic parenchyma were also resected with a hepatectomy In stage IV tumours an extended right hepatectomy was performed when possible Biliary continuity was restored by a Roux-en-Y anastomosis. If the upper margin of the bile duct showed microscopic involvement, a further resection was done if possible, otherwise the anastomosis was done on the site of section. All liver resections were carried out under total vascular exclusion[9].

Data collection

The files of all patients were analysed retrospectively. Follow-up was by routine clinical appointment or by telephone contact with the patient's doctor. Date of death was known exactly from municipal council records. Cumulative survival rates were calculated by the Kaplan–Meier method

Results

Operations performed

Eighteen resections were carried out (group 1), of which 14 proved curative on the specimen (curative resection rate). Thirteen resections were done in association with a hepatectomy (*Table 1*). The median number of blood units transfused during resection was 3 (range 0–6).

Table 1 Details of patients undergoing resection

Surgical procedure	No	Stage*	Median follow-up (months)	Status at follow-up†
Biliary resection	1–3	I, II, II	27	D, A, D
Right hepatectomy ± segment IV resection + segment I resection	4–11	IIIa	44	A, A, A, A, A, A, D, D
Left hepatectomy + segment I resection	12–14	IIIb, IIIb, IV	10	D, D, D
Palliative resection of the bile duct (nos 15, 16) with hepatectomy (nos 17, 18)	15–18	I, III+ (portal vein invaded) IV, IV	16	D, D, D, D

Patients are listed by stage· patients 1–14, curative resection; patients 15–18, positive margins *Bismuth and Corlette classification[5]. †D, dead, A, alive

Twenty-one (54 per cent) patients underwent intubation ($n = 15$), segment III intrahepatic bypass[10] ($n = 2$) or a combined procedure ($n = 4$), and formed group 2. A palliative surgical treatment was decided when laparotomy revealed malignant invasion of the main portal vein ($n = 3$), invasion of a portal vein branch contralateral to the biliary duct extension ($n = 3$), peritoneal seeding ($n = 6$), coeliac lymph node metastasis ($n = 4$) or retro-pancreatic bile duct involvement ($n = 5$). Intubation was achieved with 10-Fr polythene tubes left *in situ*, with neither end exteriorized. The distal end of the tube was placed in the duodenum in order to allow endoscopic removal in case of obstruction.

Pathology

The features of the 18 specimens removed are shown in *Table 1*. At frozen-section examination the diagnosis was confirmed and the determination of positive and negative tissue sampling was obtained. In all cases, the examination of paraffin-embedded sections confirmed the interpretation of the frozen sections. The only difficult case was a patient who had a stage IIIa lesion with portal vein invasion and who underwent a segment III bypass with stenting of the right hepatic duct. Frozen-section examination suggested the diagnosis of carcinoma but was not definite. The paraffin-embedded samples were examined by three anatomopathologists before they concluded that it was actually a malignant process. Eight years after operation, as no dissemination was found and secondary biliary cirrhosis had appeared, a liver transplantation was performed. Examination of the specimen confirmed the diagnosis of carcinoma.

Perineural invasion was present in 12 patients. Vascular invasion unilateral to the bile duct extension was present in five patients. Fourteen patients had free margins. In one case, the superior margin section was positive but a further section on non-invaded tissue was possible. Two patients had a positive superior margin at frozen-section examination. In those two patients, the superior margin had been found positive after section of the biliary duct above the tumour. Further resection of the bile duct was not possible and the operation had already passed the point of no return. The only solution was a resection with a hepatectomy. In two other cases, portal vein invasion was discovered only after section of the bile duct, and a palliative biliary resection without hepatectomy was performed.

No resection has been performed when lymph nodes from the hepatic artery or of the coeliac trunk were found positive at frozen-section examination ($n = 4$). However, two patients who had a curative resection had one positive lymph node in the hepatic pedicle found on the specimen. All the tumours resected were adenocarcinoma of the bile duct of the nodular type. In 14 patients the adenocarcinoma was well differentiated and in three it was poorly differentiated.

Early results

In the resection group (group 1), there was no hospital death (i.e. within the first 30 days after operation or related to a postoperative complication). Four patients developed postoperative complications: hepatic failure (defined as a decrease in factor V to under 50 per cent[11], persisting 10 days or more after operation; association with encephalopathy defined severe hepatic failure)

($n = 1$), pleural abscess ($n = 1$), central line sepsis ($n = 1$), and duodenal fistula ($n = 1$). Median time spent in the intensive care unit (ICU) was 2 (range 0–19) days, and median hospital stay was 22 (range 9–55) days.

In the non-resection group (group 2), three patients died, aged 56, 68 and 82 years respectively. Death was related to cholangitis ($n = 1$), multiple organ failure ($n = 1$) and aortic aneurysm rupture ($n = 1$). Non-fatal complications occurred in four other patients. Median stay in ICU was 0 (range 0–6) days and total hospital stay was 18 (range 5–54) days.

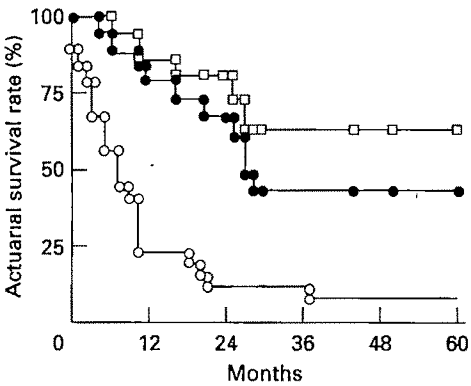
Late results

In group 1, follow-up ranged from 4 months to 12 years, and median follow-up was 26 months. The 1-, 3- and 5-year actuarial survival rates were 67, 47 and 47 per cent respectively, with a median survival time of 26 months (*Fig. 2*). If only the 14 patients with curative resection were considered, the figures for 1-, 3- and 5-year actuarial survival rates amounted to 90, 61 and 61 per cent respectively, with a median survival of 27·5 months (*Fig. 2*). Recurrence after curvative resection of the tumour occurred in six patients at a median time of 15 months. After palliative resection, the four patients died of disease at 4, 11, 20 and 28 months respectively.

In group 2, follow-up ranged from 1 month to 8 years, with a median of 7 months. All patients but one in group 2 died. The actuarial survival at 1 and 2 years was 31 and 11 per cent respectively, for a median survival of 7 months (*Fig 2*). One patient is alive 9 years after a liver transplantation carried out at 8 years for a secondary biliary cirrhosis (see above).

Quality of life could be estimated in group 1 by reporting the incidence of complications related to the procedure (irrespective of the complications due to a recurrence). Two patients had attacks of cholangitis requiring antibiotic treatment, and one patient had jaundice requiring dilatation of the anastomosis and stent placement.

In group 2, quality of life was assessed by late complications due to obstruction of surgically placed stents or stenosis of the bypass. After intubation ($n = 15$), four patients required endoscopic removal and replacement of the stent at 1, 1, 6 and 24 months; in one case, such a procedure could not be achieved and external biliary drainage was required. After bypass ($n = 6$), three patients developed anastomotic stenosis, requiring dilatation and stent placement at 3, 6 and 36 months. One of these patients underwent transplantation. In two other patients, duodenal obstruction occurred 6 months after intubation, requiring a gastrojejunostomy.



No at risk

	0	12	24	36	48	60
All resections	18	14	13	5	4	2
Curative resections	14	12	10	6	4	2
Stenting and/or bypass	18	5	2	2	1	1

Fig. 2 Actuarial survival of patients according to treatment. Each point represents a patient □, Curative resections ($n = 14$); ●, all resections (curative and palliative) ($n = 18$), ○, surgical bile duct stenting and/or bypass ($n = 21$)

Discussion

In the treatment of hilar bile duct cancer, there is general agreement to select patients for resection and to offer other patients palliation, at the potentially lower cost in terms of mortality and morbidity. However, there is a large discrepancy among experts about the extent of preoperative assessment, surgical indications and surgical techniques.

Preoperative assessment

Some contraindications to surgery, for example portal vein thrombosis, distant metastasis, or distal bilateral biliary duct extension are easily shown by a simple investigation including ultrasonography, Doppler and transhepatic percutaneous cholangiography. A further evaluation of the local extent of the tumour, i.e differentiating between tumour invasion and mere inflammation or sclerosis at the limits of the tumour, is far more delicate. It cannot rely on imaging alone[12,13] and requires a surgical dissection both for vascular involvement[14] and the exact limit of the tumoral extension on the bile duct[15]. Baer *et al.*[6] and Bismuth *et al*[5] practised an extensive preoperative evaluation including computed tomography (CT), arteriography, preoperative percutaneous cholangiography, ultrasonography and duplex, but the yield was disappointing, with a curative resection rate among the patients selected for surgery of 40 and 45 per cent respectively. These percentages are similar to those reported in this series after a limited preoperative assessment (46 per cent).

Surgical indications

Adopting the preoperative strategy described above may lead a surgeon to perform many surgical explorations and few resections. In the present series, 39 of 50 patients underwent surgery but only 14 could benefit from a curative resection. This raises a criticism from advocates of percutaneous or endoscopic procedures who claim that this policy conveys an excessive morbidity and mortality[16]. Those authors are in favour of placing stents by percutaneous approach or endoscopy in the majority of patients and reserving a few 'good cases' for surgery. However, surgical palliation with stenting or bypass does not represent a significant penalization vis à vis percutaneous or endoscopic stenting. In a comparative study, Nordback *et al.*[17] have shown that results obtained with surgical placement of large-bore silicone rubber transhepatic stents were equivalent to those obtained after non-surgical palliative procedures. In the present series, when a tumour was found to be irresectable at surgery and a surgical palliative procedure was undertaken (group 2), mortality, morbidity, hospital stay and outcome were not worse than what is reported after non-surgical palliative procedures, and the efficacy of surgically placed stents was equivalent[7]. Restricting indications of surgical exploration to the 'best cases' could deprive some patients a chance of cure. In the present series, the authors operated on a patient whose tumour was deemed irresectable and who had previously undergone placement of a transhepatic prosthesis; the tumour could be removed and the patient is now free from disease 2 years after operation.

Preoperative procedures

The mortality rate of hilar bile duct cancer surgery in the literature ranges from 5 per cent when there is no jaundice[6] to 13–28 per cent when the bilirubin level is superior to 10 mg/dl[18]. Preoperative biliary decompression has been proposed[19] to allow surgery when the bilirubin level has decreased to under 5 mg/dl[20]. Biliary decompression, however, diminishes the bile duct calibre and thickens the bile duct wall[6], making dissection and the determination of tumour borders more difficult. No study has demonstrated any advantage of such procedure on mortality or morbidity. Lai *et al.*[21], in a randomized trial comparing two groups of patients with neoplastic jaundice (one with preoperative endoscopic biliary decompression and the other without), have demonstrated that mortality and morbidity were the same in both groups. Only 25 of the 37 patients having preoperative biliary decompression had an effective drainage and 12 patients had specific complications due to this procedure.

If major hepatectomy is intended, preoperative selective portal embolization of the projected resected liver has been proposed to diminish the risk of hepatic failure and to increase the volume of hepatic parenchyma that is not removed[22,23]. If those series have demonstrated the feasibility of such procedure, there is no demonstrated advantage today.

Surgical techniques for resection

What is the goal: free margins or macroscopic clearance? It has been the authors' policy to reserve resection for cases where the tumour appeared to be accessible to complete excision with free margins, and to look carefully for any contraindication before embarking on the decisive steps of the procedure. They have relied on frozen-section examinations, although many authors feel suspicious about it[5,6]. In four cases microscopic residual tumour could not be avoided, as it was only after division of the bile duct above the tumour that it became apparent that tumoral tissue was to be left behind. However, these figures compare favourably with other surgical series where resections with positive margins or macroscopic residual tumour account for 60 per cent of all resections[5,6]. The authors of those reports claim that it is beneficial to excise the cancer whenever all macroscopic tumoral tissue can be removed, regardless of the margins[6,24]. Bismuth *et al.*[5] reported 23 resections of which only nine had free margins. There was no mortality, and the overall median survival was 20 months, which is less than in the present curative group but superior to any survival obtained after stenting or bypass surgery[6]. However, the present authors consider that palliative resection should be discussed carefully. Such resection carries a significant risk of death or major complication. Tompkins *et al.*[14], reporting the changing patterns of management of hilar cancer at their institution, showed a reduction in mortality rate from 12 to 4 per cent by more rigorous selection of patients for resection. Those resections have not demonstrated any benefit in terms of survival. Gallinger *et al.*[25], in an attempt to evaluate in the literature the impact of resection rate on survival, concluded that palliative resection was not beneficial.

Hepatic resection: when and which? Although Tompkins *et al.*[14] claim that hepatic resection is seldom required, the majority of authors perform some sort of liver resection together with the excision of the bile duct[4–6,15,24,26,27–29]. In the present series, 13 of 18 patients underwent liver resection.

This issue of liver resection should be addressed in three separate parts. First, the problem of routine segment I resection; second, the type of liver resection required in case of distal extension of the tumour (stage III); and third, the problem of stage IV tumours.

Resection of segment I. There is sizeable evidence that caudate lobe excision should be performed *en bloc* with resection of the hilar tumours. The caudate lobe is adjacent to the posterior aspect of the hilum and sends small bile ducts to the right and the left ducts and their confluence. Nimura *et al.*[26] have shown, in a series of 46 resected specimens, that caudate bile ducts were invaded in 44 of them. Ogura *et al.*[30] and Tashiro *et al.*[27] have shown significant improvement in survival after routine resection of segment I. In stage I and II lesions, routine excision of the caudate lobe is performed routinely by the present authors.

Stage III lesions. The involved side of the liver must be removed to allow a radical excision. *En bloc* excision of the caudate lobe is performed simultaneously. For stage IIIa tumour, extended right hepatectomy ($n = 4$) was performed more often than right hepatectomy ($n = 2$), as it gives better clearance. In stage IIIb tumours ($n = 2$), left hepatectomy was carried out. It might be necessary to extend the resection to the right anterior segments V and VIII in some cases[26].

Stage IV tumours. The debate is open between palliation, extended liver resection on either side, or liver transplantation[3,4]. When the tumour extends little beyond the secondary division of the left bile duct, it may be possible to do a right trisegmentectomy and an anastomosis on the canal of segment II and III. In patients where a left trisegmentectomy is required, with an anastomosis on the right posterior bile duct, difficulty is maximal. The authors did not perform this operation, and to their knowledge, it has been reported in a few series for the treatment of bile duct cancer[26]. In the present series, there were three stage IV lesions. In two cases the intraoperative evaluation estimated the stage as IIIa and it was only at frozen-section examination that the correct extension appeared. In another stage IV case a curative resection was performed, as resection of the right secondary biliary division was possible without extended left hepatectomy.

Western surgeons have proposed liver transplantation in selected cases. Ringe *et al.*[3] reported 20 patients; mean survival was 26 months, which is not different from what is obtained after resection, and details of staging are lacking, to establish any valuable comparison. When liver transplantation was performed with positive nodes, however, no survival extended beyond 16 months.

Associated procedures

Venous resection or Whipple's operation have been proposed, simultaneously with bile duct and liver resection. Nimura *et al.*[28] reported a series of 29 combined venous resections. The mortality rate was 17 per cent, mean hospital stay was 71 days, and survival rate at 1 year was 50 per cent. Tashiro *et al.*[27] reported six cases of combined venous resections with a median survival of 15 months. Tsukada *et al.*[29] performed a liver and bile duct resection combined with Whipple's operation in five patients with hilar tumours; two of the five died after operation and the three survivors died 8, 10 and 27 months later. Those combined procedures seem to increase mortality with little benefit on survival.

In conclusion, excellent results can be obtained with curative resection when it is feasible without an extended procedure. Preoperative assessment can show some contraindications, but closer evaluation of the local extent of the tumour requires a surgical exploration with tissue sampling for frozen-section examination. When curvative resection appears impossible, surgical stenting and/or bypass may represent a good alternative.

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Effect of a no-conversion policy on patient outcome following laparoscopic cholecystectomy

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Background One of the potential drawbacks of laparoscopic cholecystectomy is lack of experience with open cholecystectomy. The aim of this study was to examine the effect of a no-conversion policy on patient outcome following laparoscopic cholecystectomy.

Methods One hundred and sixty-one patients underwent laparoscopic cholecystectomy in the no-conversion period and were compared with 127 operated on during a period in which there was a low threshold for conversion from laparoscopic to open cholecystectomy. All operations in the no-conversion period were performed by surgeons in training assisted by one consultant.

Results One patient in the no-conversion group had a gallbladder carcinoma and the operation was converted to open surgery. All others underwent total cholecystectomy except for one patient who had part of a severely diseased gallbladder left *in situ*. Operating time was significantly lower, median 65 *versus* 50 min ($P = 0.004$), as was postoperative hospital stay, 3 *versus* 2 days ($P = 0.001$), in favour of the no-conversion group. There was no bile duct injury and postoperative complications were similar in both groups (6 *versus* 8 per cent; P not significant).

Conclusion Laparoscopic cholecystectomy can be performed safely without converting to open cholecystectomy. As surgeons become more experienced with laparoscopic cholecystectomy, the need to perform open cholecystectomy in an elective setting may disappear.

One of the potential drawbacks of laparoscopic cholecystectomy is lack of experience with open cholecystectomy. At present the average surgical trainee may perform between 100 and 200 cholecystectomies before taking up a consultant post, of which as few as ten to 20 would be open operations. These operations are likely to be difficult, being either conversions from laparoscopic cholecystectomy or cholecystectomy in an acute situation that require the assistance of a more experienced colleague to complete.

Conversion rates for laparoscopic cholecystectomy vary widely among surgeons. In a recent prospective audit of laparoscopic cholecystectomy, conversion rates for individual surgeons varied between 5 and 38 per cent[1]. Lack of progress after operating for 1 h is considered an indication by many to convert to open cholecystectomy. Indeed some suggest that in up to 10 per cent of patients operations should be converted from laparoscopic to open cholecystectomy in order to ensure safe cholecystectomy[2].

Since laparoscopic cholecystectomy was first described there has been a major improvement in both the instruments and video technology required to perform laparoscopic surgery. This, combined with greater experience, has made laparoscopic cholecystectomy in the acute setting, and in the situation where there may be dense adhesions to the gallbladder, a feasible option. The aim of this study was to examine the effect of a no-conversion policy on patient outcome following laparoscopic cholecystectomy.

Patients and methods

Since January 1991 data on all patients undergoing both laparoscopic and open cholecystectomy for symptomatic gallstones under the care of one consultant have been gathered prospectively (*Table 1*). During this period 360 patients underwent cholecystectomy of which 288 procedures were laparoscopic and 72 were open. Open cholecystectomy was performed either as part of a randomized controlled trial comparing laparoscopic with minilaparotomy cholecystectomy[3] (50 patients) or for patients with common bile duct stones (nine). Open cholecystectomy was also performed for a small number of patients with biliary peritonitis (four), biliary fistulas (three), necrotizing pancreatitis (two), in patients with morbid obesity undergoing vertical banded gastroplasty (three) and in one patient with severe portal hypertension.

In the period before April 1994 a low threshold for conversion from laparoscopic to open cholecystectomy was adopted. After this and with the introduction of better laparoscopic instruments, for example Maryland and right-angled dissectors and special instruments to grasp a thick-walled gallbladder, the conversion policy was changed. At that stage it was felt that dissection and demonstration of the biliary anatomy could be carried out as safely with laparoscopic operation as with open surgery and if conversion was required then subtotal cholecystectomy or cholecystostomy with stone removal would be the preferred option. It was believed that conversion for other reasons, such as intraoperative bleeding, could be avoided.

All operations in the no-conversion period were performed by surgeons in training, ranging from senior house officer to senior

Table 1 Demographic details of patients undergoing laparoscopic cholecystectomy

	Conversion	No conversion
Age (years)*	54 (40–65)	56 (43–63)
Sex (% female)	86	81
Body mass index*	25 (23–29)	26 (24–30)
Smokers (%)	38	28
Presentation (%)		
Biliary colic	70	75
Acute cholecystitis	14	12
Gallstone pancreatitis	12	9
Obstructive jaundice	2	4

*Values are median (interquartile range)

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registrar grade assisted by one consultant The degree of assistance provided by the consultant depended on the level of laparoscopic experience the trainee had For example, when trainees were early in their learning curve or commencing laparoscopic cholecystectomy, the consultant always took control of the electrocautery pedal and clipped the cystic duct and artery The consultant first assisted at all operations irrespective of the experience of the operating surgeon while a second assistant took control of the laparoscope. All patients received prophylactic antibiotics and had prophylaxis against deep vein thrombosis. Patients with pancreatitis, abnormal liver functions tests or a dilated common bile duct on ultrasonography underwent preoperative intravenous cholangiography before 1994 and after that had either preoperative endoscopic retrograde cholangiopancreatography (ERCP) or operative cholangiography Patients with acute cholecystitis were operated on during the same hospital admission when operating time was available. Laparoscopic cholecystectomy was carried out using a standard four-trocar technique except that an open method of insertion was used for first trocar in all cases. Nasogastric tubes, urinary catheters or postoperative drains were not used in any patient.

Statistical analysis

Hospital stay and operating time are expressed as median (interquartile range) and were analysed using the Mann–Whitney *U* test.

Results

In the period of low threshold for conversion, 127 patients underwent laparoscopic cholecystectomy of whom 15 (12 per cent) underwent conversion from laparoscopic to open cholecystectomy. The reasons for conversion are detailed in *Table 2*. After April 1994 in the no-conversion group 161 patients underwent laparoscopic cholecystectomy. In this group one patient's gallbladder appeared suspicious for carcinoma at laparoscopy and was biopsied. Frozen-section analysis confirmed carcinoma and a cholecystectomy with liver resection and regional lymphadenectomy was performed at open surgery. One patient had part of the wall of a severely diseased gallbladder left *in situ* after identifying and ligating the cystic duct and artery. All other patients underwent total cholecystectomy in the no-conversion group. Both hospital stay, median 3 (range 2–4) *versus* 2 (range 1–2) days, and operating times, median 65 (range 46–70) *versus* 50 (range 40–60) min, were significantly reduced ($P<0.01$) in the no-conversion period.

Table 2 Reasons for conversion in low-threshold group

	No. of patients
Adhesions	4
Severe cholecystitis	3
Ill-defined anatomy	4
Haemorrhage	3
Impacted stones	1

Table 3 Postoperative complications

	Conversion	No conversion
Bile leak	2	—
Bleeding	1	—
Sepsis	—	1
Subphrenic collection	—	1
Pelvic collection	—	1
Pancreatitis	—	1
Abdominal wall abscess	—	1
Chronic umbilical sinus	1	—
Wound infection	2	3
Pulmonary embolus	—	1
Myocardial infarct	—	1
Acute retention	—	1
Urinary tract infection	1	1
Readmission	2	1

Complications

There was no bile duct injury and no difference in complication rates between the groups (*Table 3*). There were three serious complications, two bile leaks and one postoperative bleed, in patients treated in the period of low threshold for conversion. One bile leak arose from an accessory bile duct while the other occurred because of failure to clip the cystic duct adequately. One postoperative haemorrhage occurred in a patient who had been prescribed warfarin following coronary bypass surgery some years previously. Five serious complications occurred in the no-conversion group. One patient who had part of the wall of a severely diseased gallbladder left *in situ* after laparoscopic cholecystectomy required laparotomy for sepsis 48 h after operation. Residual gallbladder mucosa and gallstones found at operation were removed. This patient's postoperative recovery was also complicated by a pulmonary embolus. A sterile pelvic collection occurred in a patient with renal failure at the tip of a Tenchkoff catheter 2 weeks after laparoscopic cholecystectomy. The catheter had become blocked after operation and attempts to free it by interventional radiology had been unsuccessful. One patient developed severe postoperative pancreatitis while another had a myocardial infarct 48 h after operation.

Retained common bile duct stones

Five patients (2 per cent) re-presented with retained common bile duct stones. All were dealt with successfully by ERCP and sphincterotomy.

Discussion

The study demonstrates that a no-conversion policy can be adopted for laparoscopic cholecystectomy without having an adverse effect on patient outcome. All operations were performed by surgeons in training and no patient with symptomatic gallstones was excluded on the basis that they had acute cholecystitis or required urgent cholecystectomy. There were no differences in complication rates between groups and no patient suffered a bile duct injury. This outcome has been made possible by the dramatic improvement in laparoscopic instruments that has occurred over the study period. Thick-walled gallbladders can now be grasped with heavy toothed instruments, while dissection in Calot's triangle can be accomplished with at least equal safety to that of open surgery by using a combination of sharp and blunt dissection with scissors, Maryland and right-angled dissectors. Intraoperative bleeding can now be controlled by use of adequate suction devices which will allow any bleeding point to be identified and ligated or cauterized as appropriate.

One of the drawbacks of laparoscopic cholecystectomy has been the twofold to threefold increase in common bile duct injury. This increase has been due mainly to the steep learning curve associated with laparoscopic cholecystectomy and there is no indication that when beyond the learning curve the common bile duct is at any greater risk than with open cholecystectomy[4]. In a statewide experience of over 30 000 cholecystectomies between 1989 and 1993 Russell and colleagues[5] demonstrated that the incidence of major bile duct injury rose significantly from 0·04 per cent in 1989 to 0·24 per cent in 1991 with the introduction of laparoscopic cholecystectomy. By 1993, however, the bile duct injury rate for laparoscopic cholecystectomy had fallen to 0·11 per cent and was no longer significantly different from that of open cholecystectomy.

Up to 16 per cent of bile duct injuries associated with laparoscopic cholecystectomy occur after conversion to open cholecystectomy[6]. It is likely that this figure will increase as surgeons become less experienced with open cholecystectomy. Cholecystostomy or subtotal cholecystectomy with complete stone removal is a safe alternative to open cholecystectomy and can be accomplished without risking injury to the bile duct by the inexperienced open cholecystectomist.

Operative cholangiography was used infrequently in this series. Operative cholangiography does not prevent common bile duct injury[4] and there is no substitute for proper and adequate demonstration of the anatomy before clipping or dividing any structure. Although 5–10 per cent of the British population are likely to have common bile duct stones, available evidence suggests that less than half of these will develop symptoms related to their stones[7]. These are dealt with adequately by endoscopic stone removal and sphincterotomy when required.

Laparoscopic cholecystectomy has recently been shown to have no advantage over small-incision open cholecystectomy in terms of hospital stay and return to normal activity in a single-centre randomized clinical trial[8]. It is likely that these results can at least in part be explained by the high conversion rate (20 per cent) for the laparoscopic group. Any advantage laparoscopic cholecystectomy has over modern open cholecystectomy is modest and will only be maintained if conversion rates to open cholecystectomy are kept at single figures.

This study shows that a no-conversion policy can be adopted for laparoscopic cholecystectomy without adversely affecting patient outcome. As surgeons become more experienced with laparoscopic cholecystectomy the need to perform open cholecystectomy in an elective setting may disappear. If this happens, inability to dissect structures in Calot's triangle and demonstrate the biliary anatomy at laparoscopy should be accompanied by conversion to subtotal cholecystectomy or cholecystostomy with stone removal rather than attempt open cholecystectomy if the surgeon is inexperienced.

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Randomized clinical trial of conventional cholecystectomy *versus* minicholecystectomy

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Background The main argument for laparoscopic cholecystectomy in preference to open cholecystectomy appears to be based on less traumatic incisions inflicted on the abdominal wall. To investigate the effects of different incision lengths on patients following elective open cholecystectomy, a randomized clinical study was conducted.

Methods In this study 130 patients were randomly assigned to undergo either open cholecystectomy through a transverse subcostal incision of mean length 5·8 cm, so called minicholecystectomy (65 patients), or to undergo conventional cholecystectomy through a paracostal incision of mean length 13·1 cm (65 patients). The perception of pain after operation was measured by a visual analogue scale. To register late complications the mean(s.d.) hospitalization period after operation was extended to 11·5(1·2) days in the minicholecystectomy group and 15·4(2·5) days in the conventional cholecystectomy group.

Results The perceived pain and analgesic requirements were found to be similar in both groups. Twelve of 65 patients in the minicholecystectomy group and four of 65 in the conventional cholecystectomy group developed wound haematoma.

Conclusion On the basis of this prospective randomized study, the hypothesis that a smaller incision length on the abdominal wall could lower the level of perceived pain, and therefore decrease the postoperative analgesic intake after minicholecystectomy, could not be confirmed.

The use of minimally invasive techniques in the surgical treatment of gallbladder disease may have the advantage of a substantially reduced hospital stay because of less pain[1,2]. Use of trocar incisions in laparoscopic cholecystectomy generally leads to early mobilization and thus earlier recovery, but only a controlled comparison of laparoscopic cholecystectomy with the established conventional operating techniques can confirm the superiority of laparoscopic cholecystectomy.

The techniques of open conventional cholecystectomy or minicholecystectomy might both compete with laparoscopic cholecystectomy in avoiding prolonged operating time and major expenses[3]. About 2000 minicholecystectomies have been published to date throughout the world[4], whereas only a few controlled randomized studies on this question[5–7] have been conducted and can be used as a reference. The objective of the present investigation was to throw further light on the extent to which minicholecystectomy might possibly define a new standard for open cholecystectomy, focusing the argument on whether or not the patient undergoing minicholecystectomy experiences less pain.

Patients and methods

Patients

From 1 March 1991 to 31 December 1994, 148 consecutive patients underwent elective cholecystectomy in this hospital. Some 130 patients fulfilled the criteria for inclusion in this trial and gave their informed consent. Patients with acute cholecystitis ($n = 3$), ductal stones ($n = 2$), secondary intra-abdominal disease and adhesions ($n = 4$) or thromboembolic disease ($n = 4$) were excluded from the study. Furthermore, patients who were more than 30 per cent overweight according to the Broca index were also excluded ($n = 5$). Randomization was carried out using presealed envelopes immediately before the operation

Cholecystectomy

Minicholecystectomy consisted of a 6-cm subcostal transverse incision with subsequent diathermy transection of the right rectus abdominus muscle. Conventional cholecystectomy employed a 13-cm subcostal incision with additional partial extension into the muscle spaces of the right lateral epigastric region. The cystic duct and artery were ligated and the gallbladder freed from the liver After inserting a drain to the right side of the wound, the peritoneum was closed with a running suture transversely with the transverse fascia. The muscles of the rectus were subsequently reapposed with musculofascial sutures with a single-button technique. Two sutures were used to appose the subcutaneous tissue and the skin was closed subcutaneously.

Analgesic requirement and antithrombotic prophylaxis

Analgesia was administered as an intravenous infusion immediately after operation and if required until 08.00 hours the following morning (500 ml 0·9 per cent sodium chloride solution containing tramadol 400 mg, droperidol 2·5 mg and metamizol 5 0 mg) On the first and second days after operation, pain relief consisted of oral paracetamol *ad libitum*. Other analgesia was not considered necessary. Antithrombotic prophylaxis was administered in all patients with low-dose heparin (3 × 5000 units subcutaneously) into the left thigh for 5 days

Evaluation parameters

The operating times (from cutaneous incision to cutaneous suture), level of subjective pain observed during 3 days, analgesic intake and any complications during the monitoring period (10 days) were documented. Subjective pain appraisal was carried out by each patient using a visual analogue scale (VAS)[8,9]. Patients reported their pain sensation levels during the daytime every 2 h. Slight pain was defined as 0–3 on the VAS, moderate pain as 4–6, and severe pain as 7–10.

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From the first day after operation, six paracetamol tablets (500 mg each) per day were given to each patient at 8 00 hours, to be taken at the patient's discretion.

Wound haematoma was defined as a local swelling with hypoechoic space occupation, subcutaneous fluid or organized mass, revealed by abdominal sonography[10].

Statistical analysis

The hypothesis was that patients who underwent minicholecystectomy would experience a pain sensation of between 0 and 3 on the VAS 2 days earlier than those who had conventional cholecystectomy. Data were analysed using Student's t test $P<0{\cdot}05$ was regarded as significant.

Results

The two groups were similar in age and other anthropometric measurements (*Table 1*). The mean incision length in the group undergoing minicholecystectomy was 5·8 (range 5–8) cm, compared with 13·1 (range 11–17) cm in the group undergoing conventional cholecystectomy. To complete the investigation, the mean(s.d.) postoperative observation period was extended to 11·5(1·2) days, i.e. at least 10 days, in the minicholecystectomy group, and to at least 15·4(2·5) days for patients who had conventional cholecystectomy in order to register all late complications. The mean(s d.) operating time was 62(16) min in the minicholecystectomy group and 58(12) min in the conventional cholecystectomy group.

Twelve of the patients who had minicholecystectomy developed wound haematoma on the third day and were treated without any complications after drainage. One haematoma in a patient in the minicholecystectomy group led to an abscess of the abdominal wall necessitating revision. Only four patients who underwent conventional cholecystectomy developed a haematoma. One patient in the minicholecystectomy group developed pulmonary

Table 1 Patient characteristics

	Minicholecystectomy ($n = 65$)	Cholecystectomy ($n = 65$)
Age (years)	52·6(14·6) (24–66)	54·1(12·2) (32–68)
Sex ratio (F:M)	45:20	42:23
Broca index	1·15(0 12) (0 87–1·23)	1·03(0 17) (0·78–1·29)
Height (cm)	168·5(5·7) (157–175)	168·4(10·7) (150–186)
Weight (kg)	74 4(6·1) (62–83)	74·9(18·1) (48–96)

Values are mean(s.d.) (range)

Table 2 Complications after minicholecystectomy and cholecystectomy from the third day after operation onwards

	Minicholecystectomy ($n = 65$)	Cholecystectomy ($n = 65$)
Haematoma	12	4
Secondary wound healing	4	1
Abdominal wall abscess	1	0
Postoperative fever	0	0
Pneumonia	1	0
Cardiac complications	1	0
Thrombosis	0	0
Thrombophlebitis	0	0

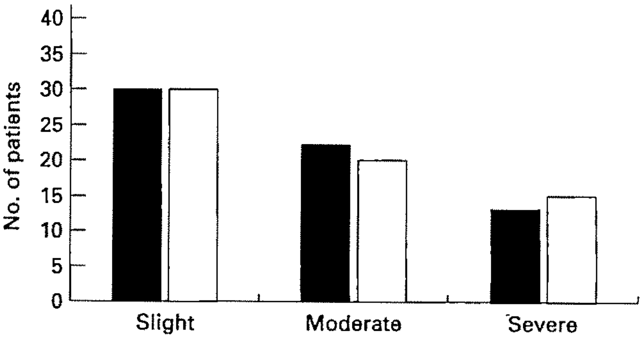

Fig. 1 Subjective sensation of pain scored by patients on a visual analogue scale (VAS) on the first day after operation. Mean(s.e.m.) scores on the VAS after minicholecystectomy ($n = 65$; ■) or conventional cholecystectomy ($n = 65$; □) were 1·24(1·02) and 1·52(0·93) respectively for those suffering slight discomfort, 4 87(0·77) and 4·89(1·30) for those experiencing moderate pain, and 6·46(0·46) and 8·67(1·13) for those in severe pain

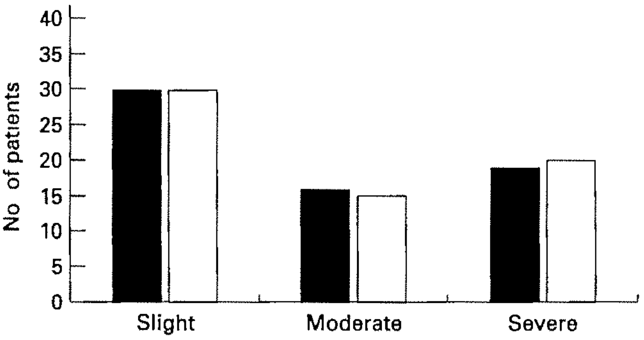

Fig. 2 Subjective sensation of pain scored by patients on a visual analogue scale (VAS) on the second day after operation. Mean(s e.m.) scores on the VAS after minicholecystectomy ($n = 65$; ■) and conventional cholecystectomy ($n = 65$; □) were 0·72(0·88) and 0·81(0 81) respectively for those experiencing slight discomfort, 4·41(1 32) and 4·31(1·14) respectively for those suffering moderate pain, and 6·29(0·36) and 7·61(0·99) for those in severe pain

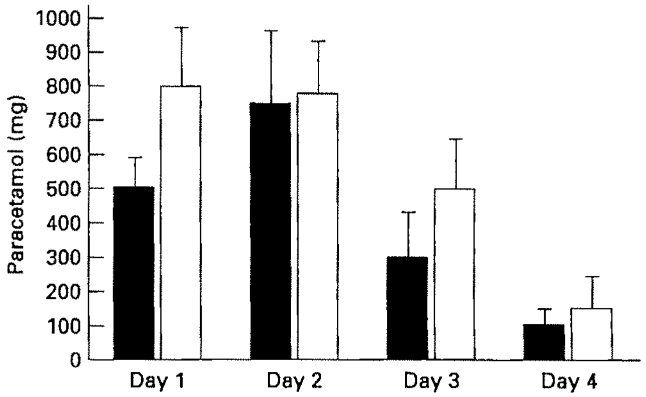

Fig. 3 Mean(s.e.m.) postoperative analgesic requirement after minicholecystectomy ($n = 65$, ■) or conventional cholecystectomy ($n = 65$; □)

infiltrates and another had angina pectoris without infarction (*Table 2*).

Pain and oral analgesic medication (*Figs 1, 2* and *3*) were similar on the first and second postoperative day in the two groups. On the fourth day after operation only ten of 65 patients in the minicholecystectomy group and three of 65 undergoing conventional cholecystectomy required a maximum of 500 mg paracetamol (*Fig. 3*).

After operation all patients were mobilized early with the help of a physiotherapist, and there was no significant difference between the two groups. As soon as the patients were allowed to drink liquids, they returned to a normal diet within 2 days.

Discussion

Until recently minicholecystectomy had only been evaluated retrospectively in about 2000 patients. Only one study compared minicholecystectomy with laparoscopic cholecystectomy[11]. All investigations were designed to establish whether less trauma to the abdominal wall (i.e. a shorter incision) leads to less postoperative pain with the objective of more rapid recovery and return to work[6,7]. At present, the laparoscopic approach has been advocated as the method of choice for cholecystectomy[11–15]. The indications for laparoscopic cholecystectomy are also being increasingly defined in acute cholecystitis, as well as in previously operated and high-risk patients[14,16,17]. The advantage of laparoscopic cholecystectomy is the better cosmetic result, reduced analgesic intake and the potentially more rapid discharge of the patient from hospital[2,11–15]. However, in all recent publications on this question laparoscopic cholecystectomy has been compared solely with open cholecystectomy. It was therefore logical to assess the technique of minicholecystectomy as a conceivably better alternative against the standard of conventional cholecystectomy with the lowest rate of complications.

The methodological prerequisite for the present study was therefore the training phase in which two surgical specialists learnt the technique of minicholecystectomy. It would have made no sense to have started a randomized clinical study without this[12,18]. Furthermore, it was important to have comparable patient groups as shown in *Table 1*.

The duration of the minicholecystectomy operation reported in the present study (62 min) is on average only 4 min longer than in conventional cholecystectomy, which is not significant. The reason for the slightly prolonged operation time may be that more time is required to prepare the site through the smaller incision and that visual control has to be changed more often. However, after the training phase use of an illuminated Harrington retractor[19] enabled a good view of the surgical site O'Dwyer *et al.*[5,20] also reported an average of 62 min for minicholecystectomy in a randomized study.

Detection of complications basically depends on how long the patient can be observed under inpatient conditions. Speedy discharge from the hospital is not *per se* an argument for or against a surgical technique[6,7], especially since a large number of complications can only be detected days later. There are no criteria which define a potential discharge time from hospital and from which the period of inpatient observation of at least 10 days (recommended during this investigation) could be decreased. It could be argued that a prolonged stay in hospital might affect patients psychologically, resulting in a significant delay in recovery. However, in this study the perceived pain, analgesic requirements and early postoperative complications in relation to the operative technique were under investigation. Under the present German National Health System patients undergoing such operations are required to have a minimum stay in hospital of 11 days to pay for the cost of the treatment.

It is noteworthy that haematomas of the abdominal wall occurred only between the third to the fifth day after operation. The incidence of haematoma in the minicholecystectomy group was high. The strong pull on the Harrington retractor in combination with the standard low-dose heparinization might explain this, since the number of reports of wound haematoma under low-dose heparinization even after minor surgical operations is increasing[10,21]. Under low-dose heparinization (3 × 5000 units), only four relevant wound haematomas were seen in the conventional cholecystectomy group. Careful traction of the abdominal wall with these retractors is required.

Surprisingly, the perceived pain as well as the intake of analgesics were the same in both groups on the first postoperative day, and these data fail to support the hypothesis that shortening of the incision by 50 per cent will result in a significant reduction in analgesic intake. These findings confirm the results of the Ulm Working Group[11]; intake of the analgesics piritramide and diclofenac in the laparoscopic cholecystectomy and the minicholecystectomy group did not differ significantly.

The present study suggests that there is no significant difference between conventional and minicholecystectomy with regard to the duration of operation, pain sensation and oral analgesic intake on the first 3 days after operation and it is therefore suggested that conventional cholecystectomy be performed as the conversion operation after laparoscopic cholecystectomy. However, if the present results are compared with those of O'Dwyer *et al.*[5] and Rohde[18], who investigated 30 patients each in randomized studies, the main argument of a rapid discharge from hospital after minicholecystectomy does not appear to be sufficient on its own to support this technique as the method of choice. Neither author found any significant differences in analgesic intake after minicholecystectomy and conventional cholecystectomy. Warren and Marais[22] compared a group of 18 patients who had minicholecystectomy with a historical group of 118 patients after conventional cholecystectomy and espoused the questionable view that shortening the duration of hospitalization is the most important argument in favour of minicholecystectomy.

Biliary tract injuries are described relatively frequently (up to 7 per cent in the learning phase) in laparoscopic cholecystectomy[4], but this has not been confirmed in large series[2]. It is relevant that this complication has not been described in the investigations so far available on the safety of minicholecystectomy. Bile duct injury occurs in 0·1–0·5 per cent of conventional cholecystectomies. Because of minimal visceral complications in this study, minicholecystectomy can only be an alternative equivalent to conventional open cholecystectomy or conversion operation where the focus is on better cosmetic results.

In summary, the hypothesis that the incision length on the abdominal wall could lower the patient's pain sensation measured on a VAS and therefore decrease the postoperative analgesic intake after minicholecystectomy could not be confirmed in this randomized study. It is suggested that minicholecystectomy cannot be regarded as a true alternative to the superior laparoscopic technique[2].

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Malignant change in the biliary tract after excision of choledochal cyst

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Background Choledochal cyst is a rare congenital condition with a high risk of malignant change if untreated. The risk of malignancy after surgical excision of choledochal cyst is not known.

Methods Forty-eight patients with choledochal cysts managed over a 21-year period were reviewed, to determine the risk of malignant change after cyst excision. Thirty-nine of 48 patients had no carcinoma at first admission; their mean(s.d.) age was 20(18) years. Thirty-seven of 39 patients underwent cyst excision and cholecystectomy followed by hepaticoenterostomy.

Results Cyst excision was incomplete in 28 of the 37 patients because dilated portions of the biliary ducts remained proximally and/or distally. In these 37 patients, no carcinoma has developed in the remnant proximal hepatic duct or the terminal bile duct after mean(s.d.) follow-up of 9·1(6·4) years. In the remaining nine patients, biliary carcinoma was diagnosed at the first visit. Six patients died from recurrence with a mean(s.d.) survival time of 13(11) months, while three patients were alive and free from recurrence 2 months, 1 year and 7 years after operation.

Conclusion Malignant change has not been observed after total or subtotal excision of choledochal cysts in this series.

Choledochal cyst is a congenital abnormality that almost invariably requires surgical intervention to prevent hepatobiliary and pancreatic complications. Many reports have demonstrated that cystenterostomy, an internal drainage procedure without resection, carries a high morbidity rate and often requires subsequent reparative operations[1–9]. Moreover, it is well recognized that the patients, either if left untreated or after internal drainage, have an increased risk of biliary tract cancer with increasing age, possibly induced by reflux of pancreatic juice into the biliary tract through the anomalous pancreatobiliary ductal junction (APBDJ) frequently associated with choledochal cyst.

Cyst excision with interruption of the abnormal ductal junction, therefore, has been advocated as the surgical treatment of choice to prevent procedure-related complications as well as to diminish carcinogenic potential. A number of surgeons have verified a considerable reduction of operative morbidity after surgical management[1,4,6–13], but a diminution in the risk of neoplastic change has not been demonstrated.

The postoperative course of 48 patients with choledochal cyst who had undergone surgery at this institution during the past 21 years was investigated. Based on these results and a review of the literature, an attempt was made to determine the risk of malignant change after cyst excision plus bile duct diversion.

Patients and methods

The medical records of 48 patients treated for choledochal cyst from July 1975 to March 1996 in this department were reviewed. Their age ranged from 21 days to 66 years, mean(s.d.) 27(20) years. Of the 48 patients, 34 were female, with a female to male ratio of 2.4. According to Todani and colleagues' classification of congenital bile duct cyst (*Fig. 1*)[14], 23 patients had type I, 21 type IV-A, and one each type II, type III, type IV-B and type V cysts. Of the 41 patients examined with endoscopic retrograde cholangiopancreatography, percutaneous transhepatic cholangiography and/or operative cholangiography, 39 were demonstrated to have an APBDJ.

Thirty-nine patients of mean(s.d.) age 20(18) years (range 21 days to 64 years) did not have biliary cancer at their first visit to this hospital (*Fig 2*). There were 29 women and ten men. Two of these patients had undergone previous internal drainage procedures (*Table 1*).

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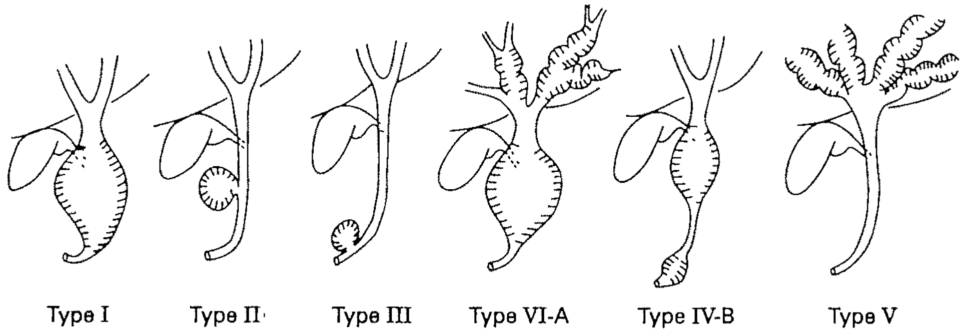

Fig. 1 Classification of choledochal cysts according to Todani *et al.*[14] Type I, extrahepatic duct cyst (single); type II, diverticulum type, type III, choledochocele, type IV-A, multiple cysts at the intrahepatic and extrahepatic ducts, type IV-B, multiple cysts at the extrahepatic duct only; type V, intrahepatic bile duct cysts

Table 1 Choledochal cyst with biliary carcinoma

Patient no.	Age (years)	Sex	Cyst type	Site of carcinoma	Previous operation	Operation	Outcome
1	63	F	I	Cyst wall	Cholecystectomy Cystojejunostomy (10 years before)	Partial resection of cyst	Died at 11 months
2	28	M	I	Cyst wall	Cystoduodenostomy (27 years before)	Left hepaticostomy	Died at 6 months
3	48	F	IV-A	Cyst wall	Cholecystectomy (15 months before)	Cyst excision and hepaticojejunostomy	Died at 22 months
4	34	F	IV-A	Cyst wall	None	Pancreatoduodenectomy	Died at 32 months
5	66	F	I	Gallbladder	None	Cyst excision with hepaticojejunostomy; cholecystectomy with gallbladder bed resection	Died at 5 months
6	33	M	IV-A	Cyst wall	None	Right extended hepatectomy; cyst excision with hepaticojejunostomy	Alive at 86 months
7	60	F	I	Gallbladder	None	Exploratory laparotomy	Died at 2 months
8	59	M	I	Cyst wall	None	Cyst excision and cholecystectomy with hepaticojejunostomy	Alive at 12 months
9	47	M	V	Intrahepatic duct	None	Right extended hepatectomy	Alive at 2 months

Nine patients (five women) with choledochal cyst had carcinoma of the biliary tract at their first visit at a mean(s.d.) age of 49(14) (range 28–66) years (*Fig. 2*). Cancer was found in the extrahepatic wall of the choledochal cyst in six patients, in the intrahepatic wall in one, and in the gallbladder in two (*Table 2*). Two patients had previously undergone an internal drainage operation, i.e. cystojejunostomy 10 years before and cystoduodenostomy 27 years previously.

All patients underwent surgical treatment in this department (*Tables 1* and *2*).

Postoperative courses were checked with hospital and outpatient medical records with special reference to the relationship between the extent of cyst excision and the manifestation of malignancy in the remaining biliary ducts. The state of health after surgery was established by telephone interview.

Results

Patients without cancer at presentation

Surgical procedures. Of 39 patients without cancer at first admission to this institution, 37 underwent cyst excision plus cholecystectomy with hepaticoenterostomy (36 with Roux-en-Y hepaticojejunostomy and one with hepaticoduodenostomy with jejunal interposition). The other two (both female, 4 months and 4 years old) had an internal drainage operation (cystojejunostomy and cystoduodenostomy) based on the chief paediatric surgeon's judgement at the time that cyst excision might be more risky (*Table 1*).

The proximal surgical line was examined in the 37 patients who had cyst excision. The biliary duct was severed above the confluence of the hepatic ducts at the hepatic hilum in one patient, at the confluence in seven, and at the level of the common hepatic duct in 29. The proximal dilated portions of the biliary ducts, intrahepatic and/or extrahepatic, remained after resection in 16 of 17 patients with type IV-A cysts and three of 17 with type I cysts; excision of the dilated proximal ducts was incomplete in 19 of 37 patients. The distal bile duct was amputated immediately proximal to the junction with the pancreatic duct in 19 patients, while some length of the distal duct, either dilated or not, was left in place in 18.

Table 2 Surgical procedures for choledochal cyst

	Without carcinoma	With carcinoma
Final procedures		
Cyst excision and Roux-en-Y hepaticojejunostomy	36*	3†
Cyst excision and hepaticojejunoduodenostomy	1	
Cystoduodenostomy	1	
Cystojejunostomy	1	
Right extended hepatectomy		2
Pancreatoduodenectomy		1
Partial cyst excision		1
Catheter left hepaticostomy		1
Exploratory laparotomy		1
Previous procedures		
Cystoduodenostomy	1	1
Cystojejunostomy	1	1
Partial cyst excision with cystojejunostomy	1	
Cholecystectomy		1

*One patient underwent left lateral segmentectomy for hepatolithiasis 2 years after cyst excision with hepaticojejunostomy, †one patient also had gallbladder bed resection

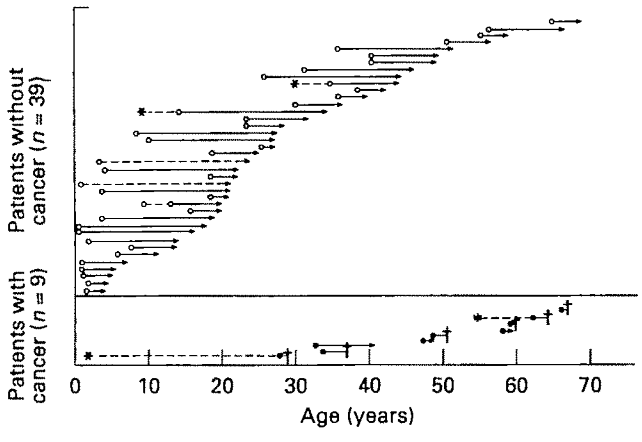

Fig. 2 Outcome of patients with choledochal cyst. Lines indicate follow-up after cyst excision (———) or cystenterostomy (– – –) following diagnosis at this (O) or another (•) institution, to the last known state of survival (→) or death (†)

Table 3 Reported cases of carcinoma developing after an excisional procedure

Reference	Year	Age when cancer detected (years)	Sex	Interval between cyst excision and detection of carcinoma	Cyst type	Site of carcinoma	Remarks
Carcinoma in proximal duct							
Thistlethwaite *et al.*[25]	1967	25	M	46 months	I	Anastomotic site	Anaplastic adenocarcinoma
Gallagher *et al.*[26]	1972	58	F	7 years	IV-A	Intrahepatic duct	Remnant intrahepatic involvement
Terauchi[27]	1978	25	M	15 years	IV-A	Intrahepatic duct	Remnant intrahepatic involvement or anastomotic stricture
Chaudhuri *et al.*[28]	1982	38	F	17 years	I (or IV-A)	Intrahepatic duct	Multiple calculi with anastomotic stricture; squamous cell carcinoma
Kaneta *et al.*[29]	1984	54	F	7 years	I	Intrahepatic duct	Multiple calculi with anastomotic stricture
Deziel *et al.*[8]	1986	—		—	IV-A	Intrahepatic duct	
Deziel *et al.*[8]	1986	—		—	IV-A	Remnant cyst wall	Insufficient excision
Joseph[9]	1990	29	M	3 years	I	Intrahepatic duct	Extensive cholangiocarcinoma
Carcinoma in distal end							
Miyoshi *et al.*[30]	1984	29		9 years	I	Distal remnant cyst wall	Insufficient excision
Kure *et al.*[31]	1984	35	M	4 years	IV-A	Head of pancreas	
Yoshikawa *et al.*[32]	1986	27	F	12 years	IV-A	Distal remnant cyst wall	Insufficient excision

Dilated portions of the biliary duct, proximally and/or distally, were left behind in 28 of the 37 patients.

Postoperative complications. There was no operative death in this series. Five patients developed early postoperative complications including cholangitis, hepatitis, bile or pancreatic juice leakage and wound infection, all of whom recovered with conservative therapy. Late complications occurred in seven patients, who suffered from ascending cholangitis, hepatolithiasis, liver abscess, pancreatitis and adhesional intestinal obstruction 1–7 years after cyst excision. Reparative surgery was required five times in four patients: reanastomosis of the hepaticojejunostomy for anastomotic stenosis in three, left lateral hepatic segmentectomy for liver abscess in one and division of adhesions for intestinal obstruction in one.

Follow-up. All 37 patients with cyst excision plus hepaticoenterostomy were alive and well in July 1996, 6 months to 21 years (mean(s.d.) 9·1(6·4) years) after surgery. All patients who had developed postoperative complications were also living a healthy life without hepatobiliary or pancreatic symptoms. None was found to have developed carcinoma in the proximal hepatic ducts or the terminal bile duct in spite of the fact that 28 of the patients still retained some portion of the involved cyst wall.

The two patients who had undergone cystenterostomy at the age of 4 months and 4 years were also asymptomatic and without evidence of malignancy 20 and 21 years respectively after the internal drainage procedure.

Patients with cancer

The nine patients with cancer underwent various operations including hepatectomy and pancreatoduodenectomy, as shown in *Table 2*, corresponding to the site and extent of cancer.

Follow-up revealed that six patients died from recurrence 2–32 (mean(s.d.) 13(11)) months after treatment. Three patients were alive and free from recurrence at 2 months, 1 year and more than 7 years after surgery. The sole long-term survivor in the present series was a 40-year-old man, who had undergone complete cyst excision and right extended hepatectomy with Roux-en-Y hepaticojejunostomy for treatment of a minute focus of cancer arising from the cyst wall. He was doing well with no recurrence or new tumour in the remaining biliary tract 7 years after operation.

Discussion

Babbitt and associates[15,16] proposed in 1969 that choledochal cyst might be closely associated with APBDJ which would allow pancreatic juice to reflux freely into the common bile duct, producing cyst formation and recurrent bouts of cholangitis. In fact, an APBDJ was observed in 39 of 41 patients with choledochal cyst in the current series, similar to Komi and colleagues' statistics (412 of 457; 90·2 per cent)[17]. An APBDJ has also been linked by other authors to the pathogenesis of biliary cancer related to choledochal cysts[18,19]. Although the carcinogenetic mechanism is not fully understood, pancreatic juice reflux into the biliary duct, combined with cholestasis and repeated bacterial infection, may play an important role in provoking malignant change of the biliary epithelium.

Two large collected series of choledochal cysts and associated biliary carcinoma come from Japan[17,20]. The incidence of biliary cancer associated with choledochal cysts ranged from 8·4 to 17·5 per cent of patients, and had a tendency to increase with age (*Fig. 3a*)[17]. The present study showed a similar figure of 19 per cent (nine of 48

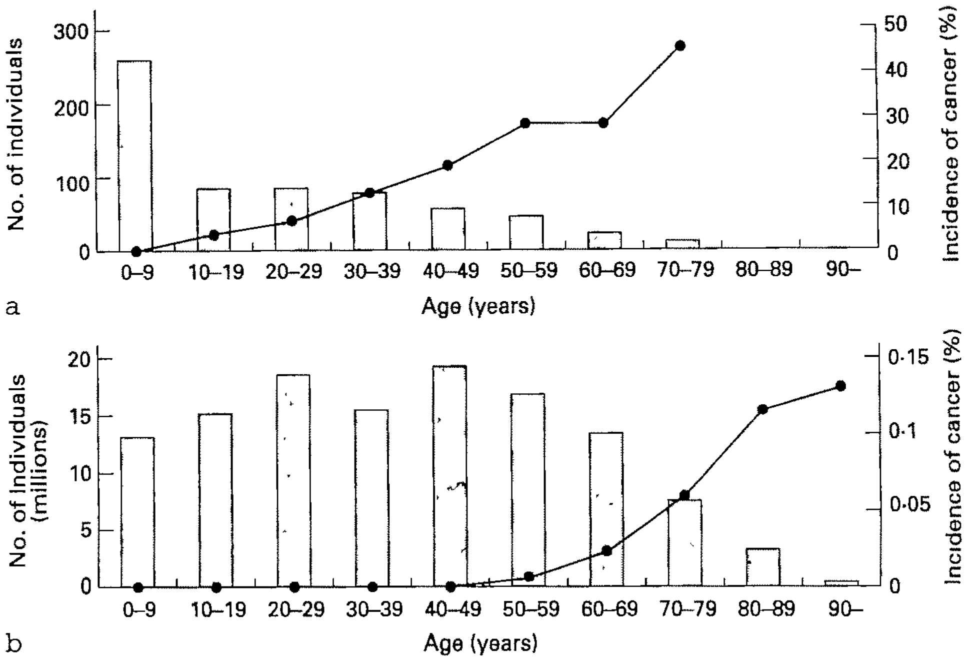

Fig. 3 Incidence of biliary carcinoma in a patients with choledochal cyst[17] and b the general population[21]. The number of people in each age group (▨) and incidence of cancer (●) are shown

patients). Comparison of Komi's statistics[17] with the age-adjusted annual death rates from biliary tract cancer in Japan demonstrates that the incidence of cancer in patients with choledochal cyst is 1000–2000 times higher than that of the general population (*Fig. 3b*)[21].

The larger series of choledochal cysts indicate that malignancy almost exclusively involves the cyst wall and the gallbladder, sparing the non-dilated bile duct in the liver[17,20]. This seems to imply that stagnation of bile flow may contribute to neoplastic changes in the dilated locations, as explained in part for occasional carcinogenesis in patients with hepatolithiasis and Caroli's disease[22,23].

Several researchers have pointed out a higher risk of cancer occurrence after internal drainage which would be expected to relieve stagnation of bile flow[3,6,18,20,24]. Todani *et al.*[30] reported that patients with previous internal drainage developed cancer at a mean age of 35·6 years, approximately 10 years after cystojejunostomy or cystoduodenostomy. This average age of cancer development was thought to be 15 years earlier than that of patients with cancer who had not undergone previous drainage surgery. In the present study, two of the seven patients who had undergone internal drainage 3–27 years previously had cancer in the cyst wall. Therefore, internal drainage apparently fails to lessen and may even augment the risk of malignant change despite alleviation of cholestasis. Aggravating factors in this setting may include reflux of intestinal bacteria and enzymes into the bile ducts through the enteric anastomosis, thus incurring biliary infection and activation of pancreatic proenzymes within the otherwise intact lumen.

In 1970, Kasai and co-workers[13], after successfully performing cyst excision in nine patients without a death, maintained that choledochal cysts should be removed and replaced with hepaticojejunostomy in Roux-en-Y fashion, even in children, to reduce postoperative morbidity and to prevent cancer occurrence. This concept has gradually gained wide acceptance throughout the world over the past few decades.

The problem remains of how to treat the biliary tracts of patients with both extrahepatic and intrahepatic cystic change, as in type IV-A lesions. Whether to perform excision of the extrahepatic cyst alone or complete cyst excision with or without hepatectomy is not resolved. Kagawa and co-workers[5] reported that carcinoma existed in the dilated intrahepatic ducts in nine of 20 patients with type IV-A-associated cancer before treatment.

To the best of the authors' knowledge, however, only eight patients have been reported in the world literature to have developed cancer in the intrahepatic ducts after apparently insufficient cyst excision followed by biliary diversion (*Table 3*)[8,9,25–29]. The interval between cyst excision and detection of carcinoma ranged from 3 to 17 (mean 9) years. This suggests that a minute occult carcinoma remaining in the cyst wall may have developed into a manifest malignant lesion in the postoperative course, or that the cyst epithelium with any 'malignant potential' may have developed *de novo* cancer with further progression into an observable malignancy.

A similar concern relates to the resection line of the distal end of the choledochal cyst. The authors were reluctant to dissect the lowest part of the cyst in 18 of 37 patients for fear of postoperative complications such as pancreatic fistula and severe pancreatitis. According to the literature, three patients acquired cancer in the distal remnant cyst wall after 4, 9 and 12 years following insufficient excision of choledochal cysts[30–32].

Although radical cyst excision appears to be the treatment of choice, the morbidity of extensive dissection in the porta hepatis or in the area of a pancreaticobiliary junction must be considered. For this reason, dilated portions of intrahepatic ducts and distal portions of bile ducts were left if dissection was difficult. Hepatectomy and pancreatoduodenectomy were reserved for those patients with carcinoma. As a result, 28 of 37 patients without cancer had an incomplete excision. Nevertheless, none of the patients, whether undergoing complete or incomplete resection, has developed cancer during follow-up of up to 21 years. Postoperative courses have also been satisfactory.

These results suggest that the risk of malignant transformation or the possibility of an occult cancer growing into a clinically manifest tumour seems to be low enough to justify the surgical strategy of excising the bulk of the cyst and of performing hepaticojejunostomy and interruption of the APBDJ. It should be possible to draw a definite conclusion about the chances of malignant change occurring after surgery after another 20 years when most of these patients reach the age of 40 years, which is accepted as the usual age for cancer occurrence in choledochal cysts[17,20].

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Variable management of soft tissue sarcoma: regional audit with implications for specialist care

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Background The aim of this study was to determine how and by which specialties patients with soft tissue sarcoma are investigated and treated within a single large health region and with what outcomes and implications for resource uptake.

Methods By retrieving the records of 377 patients with primary soft tissue sarcoma treated in the South-East Thames Region between 1986 and 1992, the presentation, investigation, treatment and outcome were compared with defined criteria for optimal management. Patient management was assessed and compared between specialties and districts on the basis of outpatient time, appropriate use of radiological investigations and preoperative biopsy, type of surgery, content of the pathology report and the incidence of local recurrence, metastasis and death over a mean follow-up period of 2·5 years.

Results Most patients (53·6 per cent) were treated by general surgeons, irrespective of tumour location. Overall only 21·3 per cent of patients were investigated optimally with wide variation among specialties. Only 60·0 per cent were treated adequately (wide excision or surgery with radiotherapy). Uptake of adjunctive therapy and follow-up were variable. Outcome was poorer in patients having a marginal excision and recurrence.

Conclusion Investigation and management of many patients with soft tissue sarcoma was both variable and suboptimal. This has implications for patient care, resource uptake and costs. As has been amply demonstrated elsewhere, patients with sarcoma are more appropriately managed in specialist centres.

Soft tissue sarcomas account for about 1 per cent of all malignant neoplasms. Lack of experience outside specialist centres poses difficulties for both pathologist and clinician, leading to wide variation in treatment and uptake of resources. In view of the current debate advocating, on the one hand, increasing use of local services and improvement of the skills base, against the recent importance attached to specialized oncology care, it was decided to audit patterns of diagnosis, treatment and outcome for patients with soft tissue sarcoma within South-East Thames Region in a recent 5-year period. The purpose of the study was to assess variations in treatment and use of resources between specialties and districts.

Patients and methods

With approval of Regional Specialty Subcommittees in Histopathology, General Surgery, Orthopaedics and Plastic Surgery, surgeons, oncologists and pathologists were approached for consent to use hospital records of patients under their care for the purpose of audit data collection. In individual cases consultants were also contacted in Dermatology, Accident and Emergency, Maxillofacial Surgery, Gynaecology, Paediatrics and Cardiothoracic Surgery, and appropriate consent was obtained Overall 232 consultants gave informed consent.

Patients were included in the audit by: (1) direct notification from consultants, (2) review of cancer registry data; and (3) searching pathology records in individual hospitals. All data concerning patients and consultants were stored confidentially on a coded numerical basis.

Criteria for inclusion

Patients were diagnosed and/or treated for a newly recognized primary soft tissue sarcoma within South-East Thames Region between 1986 and 1992. Tumours of bone, viscera and central nervous system were excluded. Cases of Kaposi's sarcoma were also excluded, because this lesion has distinctive demographic characteristics and may not even be neoplastic.

Criteria were formulated to define optimal management of a mass over 5 cm in diameter situated in subcutaneous or deep soft tissue. Recorded data were compared against these criteria.

Criteria for optimal clinical examination and investigation. These were: (a) clinical size and depth of the mass to be recorded; (b) computed tomography (CT) or magnetic resonance imaging (MRI) of the mass: (c) chest radiograph or CT scan to identify metastasis or intercurrent disease; and (d) preoperative biopsy (incisional or needle) preferably by the operating surgeon

Criteria for optimal surgical management. The main criterion was that operation should be carried out by either a consultant surgeon or senior registrar. The aim of primary surgery should be to perform wide excision with 1–2-cm margins where possible. Second, marginal or incomplete excision should be followed by further appropriate treatment

Criteria for optimal histopathology report. The report should describe: (a) the histological diagnosis; (b) the status of the resection margins; (c) the grade of the tumour; and (d) the size of the tumour.

All pathology reports were reviewed. Original pathological materials were requested in some cases to clarify diagnosis,

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status of resection margins or when clinical and pathological data did not correspond.

Patients

Four hundred and eighty-nine patients were identified. Of these, 22 cases submitted by pathologists were excluded because the treating consultant did not give consent; nine other cases were private patients and in 45 cases the notes could not be traced.

The case notes of the remaining 413 patients were collected, following which a further 36 cases were excluded – three because of unidentified primary site, seven with recurrent disease, nine for ineligible anatomical location; four with substantial amounts of unavailable data. Eight cases had been reclassified as other than sarcoma following specialist referral. Five patients were excluded following pathological review, because they had metastatic carcinomas.

Pathological blocks or slides on 96 cases (23·2 per cent) were requested for review. Material on 90 cases was received, leading to exclusion of five which were metastases. As an incidental finding of the histological review, 20 cases were subsequently reclassified (seven as a malignancy other than sarcoma and 13 as benign). Because these cases had been treated as sarcomas they were included in the analysis of treatment, but excluded from the survival analysis.

Statistical analysis

All tables were analysed with the χ^2 test. The time between events was analysed with the Kruskal–Wallis non-parametric test. Survival data were analysed using a Cox proportional hazards model[1].

Results

Data on 377 eligible patients with a diagnosis of primary sarcoma were audited. Some 202 patients (53·6 per cent) were treated primarily by general surgeons, 102 (27·1 per cent) by orthopaedic surgeons, 19 (5·0 per cent) by plastic surgeons and 54 (14·3 per cent) by a wide variety of other specialists.

The mean patient age was 56 (range 1–96) years. As anticipated, incidence increased progressively with age; 203 patients (53·8 per cent) were male and 174 (46·2 per cent) were female. The anatomical distribution is shown in *Table 1*.

The median time from first symptom to first hospital appointment was 3 months (range 1 month to 3·3 years) (*Table 2*). There were significant differences between districts in the delay between first symptom and first hospital appointment (district X median 6·5 months; district Y median 1 month). There was no significant difference between specialties.

The median time between first hospital appointment and date of first treatment was 3 weeks (range 1 day to more than 12 weeks). There were no significant differences between districts or specialties.

Preoperative investigations before definitive surgery

In all large deep-seated lesions where sarcoma might reasonably have been suspected, data for clinical investi-

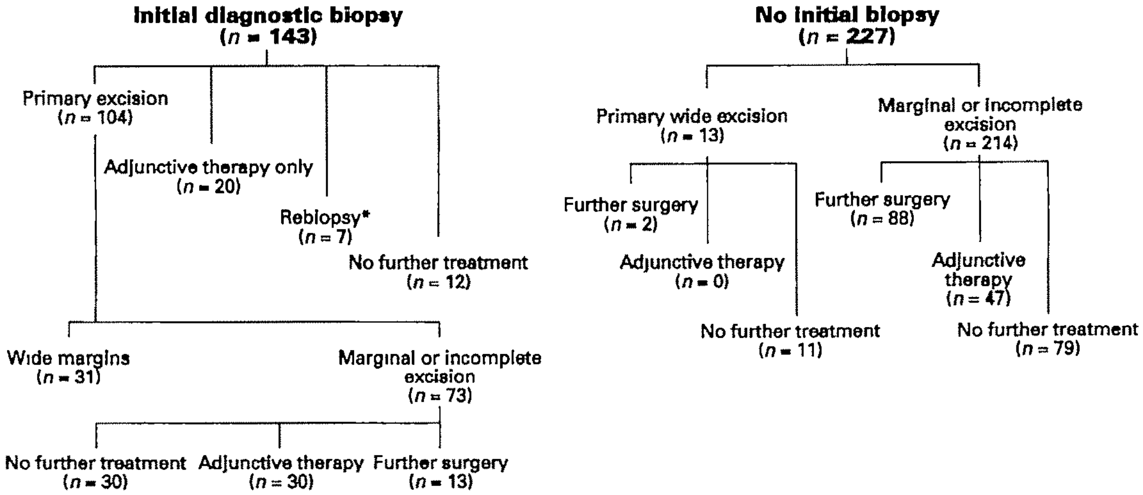

Fig. 1 Surgical management of 370 soft tissue sarcomas in the South–East Thames region between 1986 and 1992

Table 1 Primary tumour sites related to treating specialty

Site	General surgery	Orthopaedic surgery	Other	Total
Lower limb girdle	18 (67)	5 (19)	4	27
Lower limb	58 (41·4)	71 (50·7)	11	140
Upper limb girdle	20 (65)	6 (19)	5	31
Upper limb	18 (44)	15 (37)	8	41
Abdominal	35 (78)	0 (0)	10	45
Trunk	41 (66)	4 (6)	17	62
Head and neck	11 (39)	1 (4)	16	28
Thorax	1 (33)	0 (0)	2	3
Total	202 (53·6)	102 (27·1)	73	377

Values in parentheses are the percentage of cases at that anatomical site treated by that surgical specialty

Table 2 Time from date of first symptom to first hospital appointment

Time (months)	No of patients
<1	29 (9·7)
<2	48 (16·1)
<3	50 (16·8)
3–6	76 (25·5)
7–12	42 (14·1)
>12	53 (17·8)

Values in parentheses are percentages

gations were compared with the criteria for optimal preoperative investigations. There were 207 patients with complete data concerning investigations: 131 patients (63·3 per cent) did not have CT or MRI of the primary tumour; 75 (36·2 per cent) did not have chest radiography or CT before surgery; 83 (40·1 per cent) did not have a biopsy before supposed definitive surgery. Only 44 patients (21·3 per cent) fulfilled all the criteria for optimal investigation; importantly 54 (26·1 per cent) had no investigations before primary surgery. Use of plain radiography or CT of the tumour site and CT of the chest showed statistically significant differences between specialties. CT or MRI scanning of the primary site was performed in 46 patients (45·1 per cent) treated by orthopaedic surgeons *versus* 49 (24·3 per cent) treated by general surgeons ($P = 0·0002$). CT of the chest was performed in 23 orthopaedic patients (22·5 per cent) *versus* 12 general surgical patients (5·9 per cent) ($P < 0·0001$).

Patterns of treatment

Pattern of treatment was broken down according to whether or not a biopsy was performed before definitive surgery (*Fig. 1*); seven patients had neither a biopsy nor surgery.

First surgical procedure. Primary surgical excision was performed in 331 patients of whom 104 had undergone preceding biopsy. Only 56 patients (16·9 per cent) undergoing their first surgical procedure (with or without preceding biopsy) had a primary wide excision; 230 (62 per cent) of the first surgical procedures (excision or biopsy) did not meet the criteria for grade of surgeon.

Second surgical procedure. One hundred and four patients underwent a second surgical resection. At this stage an additional 53 patients had a wide excision; 84 (80·8 per cent) were operated on by a consultant or senior registrar.

Of the remaining 222 patients (67·1 per cent) who did not have wide surgical margins, 101 (45·5 per cent) received postoperative radiotherapy.

Histopathological aspects. Tumours were classified as follows: malignant fibrous histiocytoma, 79 cases (21·0 per cent); liposarcoma, 71 (18·8 per cent); leiomyosarcoma, 58 (15·4 per cent); dermatofibrosarcoma, 47 (12·5 per cent); malignant peripheral nerve sheath tumour, 29 (7·7 per cent); synovial sarcoma, 15 (4·0 per cent); rhabdomyosarcoma, 13 (3·4 per cent); other specified type of sarcoma, 39 (10·3 per cent); and unclassified sarcoma, 26 (6·9 per cent). Grade (including amount of necrosis) was the detail most commonly missed from histology reports and was not mentioned in 162 cases (43·0 per cent). Histological diagnosis was stated in 333 cases (88·3 per cent); tumour size was mentioned in 329 (87·3 per cent). The distance to resection margins was mentioned in 291 cases (77·2 per cent).

Table 3 Comparison of local recurrence rate in patients undergoing wide or marginal excision

	Wide	Marginal	Total
Local recurrence	19 (14·2)	53 (41·4)	72 (27·5)
No local recurrence	115 (85·8)	75 (58·6)	190 (72·5)
Total	134 (100)	128 (100)	262 (100)

Values in parentheses are percentages. $\chi^2 = 24·33$, 1 d.f., $P < 0·001$

Adjunctive therapy

Some 137 patients (36·3 per cent) received adjunctive therapy, of whom 20 had no surgery: 109 received radiotherapy alone, 14 had chemotherapy alone, and 14 received both chemotherapy and radiotherapy. Median time from last surgery to first adjunctive treatment was 5 (range 1·5–17·3) months.

There was a significant difference ($P < 0·0001$) between specialties in the referral rate for adjunctive therapy. Orthopaedic surgeons referred 51 patients (50·0 per cent of all orthopaedic patients in the study), general surgeons referred 53 (26·2 per cent) and plastic surgeons referred two (11 per cent).

Follow-up

Some 243 patients (65·7 per cent) were alive at the end of June 1993; 127 (34·3 per cent) had died. Only seven patients were lost to traceable follow-up. Mean follow-up was 2·5 years (range 0·2 months to 7·5 years).

Forty-four patients (11·9 per cent) had no hospital follow-up after the definitive surgical procedure. Median time between date of discharge and first follow-up appointment in the remaining 333 patients was 3 weeks (range 2 days to 5 months). Median number of follow-up appointments was 4 during the first year following surgery. In the second to fifth years of follow-up the median number of appointments annually was 2. There were no significant differences between specialties or districts.

Recurrence and metastasis. Local recurrence occurred in 101 patients (26·8 per cent). Of these, 27 patients had more than one local recurrence. Median time between diagnosis and first recurrence was 9·5 months; 57·9 per cent of recurrences occurred within 12 months of diagnosis. Fifty-five patients (14·6 per cent) developed distant metastases, the low metastatic rate reflecting the relatively short length of follow-up. In 25 patients both local and distant relapse occurred. Distant metastases were present at the time of presentation in 19 patients.

Surgical outcome

Comparison of the rate of local recurrence, distant metastases and death between patients who had a marginal excision only *versus* those who had wide local excision (at first or second surgical procedure) showed statistically significant differences (*Tables 3* and *4*). Clearly this often reflects the negative influences of large tumour size and difficult anatomical location.

Table 4 Comparison of mortality rate in patients undergoing wide or marginal excision

	Wide	Marginal	Total
Dead	22 (16·3)	53 (42·4)	75 (28·8)
Alive	113 (83·7)	72 (57·6)	185 (71·2)
Total	135 (100)	125 (100)	260 (100)

Values in parentheses are percentages $\chi^2 = 21 \cdot 55$, 1 d.f., $P < 0 \cdot 001$

Table 5 Survival analysis of 377 primary soft tissue sarcomas incorporating local recurrence as a variable

Variable	Hazard ratio*	χ^2	P
Age (years)†	1·02 (1·01–1·03)	14·30	0·0002
Recurrence			
None	1·00	35·66	<0·0001
Local	1·62 (0·93–2·84)		
Distant (metastasis)	4·49 (2·72–7·41)		
Tumour size (cm)			
<10	1·00	36·59	<0·0001
>10	1·78 (1·04–3·07)		
Not stated	4·85 (2·92–8·04)		
Histology			
Not liposarcoma	1·00	5·29	0·021
Liposarcoma	0·53 (0·29–0·94)		
Presence of mass (months)			
<12	1·00	11·48	0·0007
>12	0·37 (0·20–0·71)		

Values in parentheses are 95 per cent confidence intervals *A hazard ratio of more than 1 indicates that the variable is positively associated with death. †Age was measured as a continuous variable

Survival analysis

Variables analysed in relation to survival were: age, histology (malignant fibrous histiocytoma, liposarcoma, leiomyosarcoma or other), time from first symptom to date first seen, surgical procedure (wide excision, marginal excision, piecemeal excision or amputation), tumour size (less than 5 cm, 5–10 cm, greater than 10 cm or not stated), recurrence (none, local or distant), surgical specialty (orthopaedics, general surgery, plastic surgery or other) and preoperative duration of tumour (less than 3 months, 3–12 months, greater than 12 months or not stated). Survival time was taken to be the interval from diagnosis of primary tumour to date of death, and time to censoring as the interval from date of diagnosis to date last seen. The Cox proportional hazards model was used to examine the influence of each of the above factors on survival. Backwards stepwise elimination was used to obtain a final model in which all variables were significant at the 5 per cent level (*Table 5*). There was no significant association between outcome and surgical specialty.

Discussion

The purpose of this audit was to provide baseline information about diagnosis and management of soft tissue sarcomas in a large health region. The incidence of adult soft tissue sarcoma is known to rise with age[2] and this was reflected in the audit population. The distribution of cases by site was as expected, with almost two-thirds arising in the limbs or limb girdles. However, the anatomical distribution did not correlate with treatment by specialty, which showed that orthopaedic surgeons treated only 27·1 per cent of the total cases whereas general surgeons treated 53·6 per cent, despite the striking predominance of limb tumours. Orthopaedic surgeons treated only 97 tumours (40·6 per cent) occurring in the limbs or limb girdles, whereas general surgeons treated 114 tumours (47·7 per cent) in these locations

The significant differences between districts in the delay from first symptom to the first hospital appointment cannot be explained simply by factors external to the hospital and may indicate differences in length of the waiting lists and/or differing priorities for referrals within the region. However, once the patient had been seen at a hospital, there were no significant differences in the time interval before treatment began. Significant differences between specialties were seen in the utilization of optimal radiographic investigations, with orthopaedic surgeons showing a greater uptake of available resources. This differential use of resources not only has cost implications for hospitals or Trusts but may also have diagnostic and prognostic implications for patients. This may indicate the need for the introduction of standardized consensus protocols for investigation and management of these relatively uncommon cancers.

Investigations before surgery were judged according to the criteria described herein. Within the subset of patients who had a clinically suspicious mass, 26·1 per cent had not undergone any form of radiological investigation before primary surgery. It was also found that a diagnostic biopsy was not performed in 40·1 per cent of the patients in this audit. Preoperative clinical investigation and biopsy are an essential part of achieving a good surgical result in patients with soft tissue sarcoma[3–8], while minimizing invasive procedures. The lack of preoperative investigation might explain why only 16·9 per cent of patients had an initial primary wide excision. It is generally accepted that optimal treatment for soft tissue sarcoma is (if feasible) a minimum of a wide excision at primary surgery, or at least reoperation to increase excision margins. Alternatively adjunctive therapy should be used as a second line of treatment to reduce the rate of local recurrence[9–13]. It is notable that 222 (67·1 per cent) of all patients undergoing surgery were left with an unsatisfactory margin. Given that close margins are often inevitable (for example in the retroperitoneum or close to neurovascular or osseous structures in the limbs), it is of greater concern that, following a marginal excision, more than 50 per cent of patients with unsatisfactory margins did not receive any further treatment, thereby increasing the risk of local recurrence. Analysis of patients who had a marginal excision compared with those who had a wide excision shows a significant increase in the rate of local recurrence and death among patients in whom initial marginal surgery was not supplemented by further treatment. However, excision status was not significantly associated with survival when other variables were taken into account (*Table 5*). Recent findings[14–16] indicate that the link between local recurrence and distant metastasis is far from direct and both variables may reflect simply the intrinsic biology of the tumour. Obviously, however, local recurrence should be prevented by adequate primary treatment where possible, in order to minimize the resource implications and effect on the patient of subsequent treatment if the tumour recurs.

Almost two-thirds of patients were treated initially by a surgeon below the status of senior registrar. This may be an indication that soft tissue masses are not taken sufficiently seriously, or at least that there is a lack of clinical awareness of the possibility of malignancy at the time of presentation. The dictum that subfascial masses greater than 5 cm in diameter should be regarded as sarcoma until proven otherwise seems often to be forgotten.

Assessment of histology reporting showed that, while tumour size (87·3 per cent of cases), diagnosis (88·3 per cent of cases) and status of the resection margins (77·2 per cent of cases) was stated most frequently, the tumour grade, an important factor in determining prognosis and management[17,18], was included less frequently (43·0 per cent of cases). This has implications for clinicians attempting to plan optimal care, at least in a specialist environment. The time taken to diagnose a minority of pathological specimens was longer than desirable (data not shown), but in some cases delayed diagnosis related to the need for specialist opinion or special diagnostic techniques.

Some 11·9 per cent of patients did not receive any hospital follow-up. For those who had follow-up, the time intervals and number of appointments per year were satisfactory. The maximum time to the first follow-up appointment was 5 months. Given that 34·7 per cent of the patients with local recurrence suffered their first recurrence within 6 months of the date of diagnosis, one may speculate that inadequate follow-up may delay treatment of a local recurrence.

To summarize:

1 There appears commonly to be a low index of clinical suspicion for soft tissue sarcoma at presentation, which may affect the quality of initial investigation and treatment.
2 The consequences for the patient of local recurrence and financial implications for the treating hospitals or Trusts do not often seem to be considered. This may account for the high proportion of cases left with unsatisfactory margins but without further treatment.
3 Histopathology reporting is generally good but information on grading is often omitted; this may have implications for tumour management.
4 There is a frequent mismatch between the specialty of the treating surgeon and the site of the primary tumour. This need not matter so long as the surgeon is well practised in sarcoma management but, in a non-specialist setting, unfamiliarity with the tumour type, the anatomy, and the therapeutic and function-preserving options may result in suboptimal care.
5 Apparent variations between specialty and districts with regard to uptake of investigations and use of adjuvant therapy suggest significant resource implications and a need to develop more standardized guidelines.

In conclusion, all of these findings add support to the concept, already well demonstrated in Sweden[9,19] and promulgated elsewhere[20], that soft tissue sarcomas are managed most appropriately in specialist centres.

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Carotid plaque characteristics and presenting symptom

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Background The importance of identifying features of carotid artery disease, in addition to degree of stenosis, which predict subsequent stroke is becoming increasingly clear. This study assessed the relationship between carotid plaque characteristics and presenting symptoms.

Methods Some 285 symptomatic (transient ischaemic attack (TIA) 127, amaurosis fugax 58, transient stroke 15, established stroke 55, progressive stroke 11, crescendo TIA 19) and 65 asymptomatic patients were studied with colour-flow duplex imaging. All patients had 60–99 per cent internal carotid stenosis. Carotid plaque morphology (classified according to Gray-Weale) and plaque surface features were assessed.

Results Plaque types I and II were more common in symptomatic patients (83 per cent *versus* 44 per cent; $P < 0{\cdot}0001$). Plaque surface was classified as smooth (34 per cent), irregular (44 per cent) or ulcerated (22 per cent). Ulceration was also more common in symptomatic patients (23 *versus* 14 per cent; $P = 0.04$). In symptomatic patients there was no association between presenting symptom and plaque morphology or surface features ($P = 0{\cdot}9$ and $P = 0{\cdot}8$ respectively). On multiple regression analysis plaque morphology did not distinguish between patients who presented with stroke without warning and other symptomatic patients (who had TIA, amaurosis fugax, crescendo TIA or stroke with warning).

Conclusion There was an association between echolucent type I and II carotid plaques and the presence of symptoms but not their type. Plaque morphology was not characteristic in a subgroup of patients who had stroke without warning. Further prospective study of plaque morphology in asymptomatic patients might help identify high-risk groups.

Symptomatic atheromatous carotid artery disease is believed to result from local thrombosis at the site of an atherosclerotic plaque followed by cerebral embolization[1]. Many factors influence whether a carotid plaque causes symptoms, including local plaque characteristics, the state of the cerebral circulation and systemic factors such as procoagulant tendencies. To date, the principal factor which identifies high-risk plaques is the severity of carotid stenosis[2,3]. Other factors, however, must be important, since patients with symptomatic carotid stenoses are at much greater risk of subsequent stoke than patients with asymptomatic carotid stenoses of similar severity[2–7].

Previous studies have suggested that the carotid plaque characteristics are different in symptomatic and asymptomatic patients[8–10]. It has also been suggested that different plaque types may favour different clinical presentations, for example amaurosis fugax rather than transient cortical ischaemia[11]. The aim of this study was to assess carotid plaque characteristics in a group of asymptomatic and symptomatic patients with 60–99 per cent carotid stenosis, in order to assess if there was any association between carotid plaque type and presence or type of cerebral symptoms.

Patients and methods

From 1987 to 1995, 285 patients with a symptomatic 60–99 per cent carotid stenosis were identified. Classification of presenting symptom was performed by a consultant neurologist and based on Millikan and colleagues' classification and outline of cerebrovascular diseases[12,13]. The presenting symptom was defined as amaurosis fugax (unilateral transient blindness), transient ischaemic attack (TIA, focal neurological deficit lasting less than 24 h), transient stroke (focal neurological deficit lasting more than 24 h but less than 3 weeks), established stroke (focal neurological deficit lasting more than 3 weeks), progressive stroke (a progression of a neurological deficit over at least 24 h) or crescendo TIA (a succession of TIAs in which succeeding TIAs are more severe or frequent)[14]. To highlight a group of patients who suffered a stroke without previous neurological warning events, patients were questioned carefully regarding any symptoms preceding the development of stroke. Patients' symptoms were further defined as non-stroke symptoms (amaurosis fugax, TIA and crescendo TIA; $n = 204$), stroke with warning (patients who had any preceding transient neurological event in the past 6 months; $n = 5$) and stroke without warning (patients without a preceding neurological event; $n = 76$).

Over a similar interval 65 patients with symptomatic peripheral vascular but no cerebrovascular symptoms were found to have an asymptomatic 60–99 per cent internal carotid stenosis and included in the study.

Degree of stenosis was assessed using Doppler frequency shift and velocity criteria (Ultramark 9, HDI, Advanced Technology Laboratories, Washington, USA), plaque morphology was classified according to Gray-Weale and colleagues[15] as type I (echolucent) to type IV (echogenic) and plaque surface graded as smooth, irregular or ulcerated (*Fig. 1*). Ulcers were defined as plaque surface craters of 2 mm or more.

Data were collected prospectively and stored on Dbase 4 (Borland, Scotts Valley, California, USA) and statistical analysis carried out on Statview (Abacus Concepts, Berkeley, California, USA). The relationship between plaque characteristics and presentation was assessed by contingency tables using χ^2 and by multivariate analysis (dependent variable: symptoms; independent variables: age, sex, degree of carotid stenosis, plaque morphology and surface characteristics). The relationship between plaque morphology and patient-related variables was assessed by multivariate analysis, plaque morphology being the dependent variable and age, sex, degree of internal or common carotid stenosis, ischaemic heart disease, hypertension, diabetes mellitus and plaque surface acting as independent variables

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Results

The mean age of the patients was 68 (range 38–90) years; 238 (68 per cent) were men, 88 (25 per cent) were current smokers, 128 (37 per cent) had symptomatic ischaemic heart disease, 173 (49 per cent) had evidence of peripheral vascular disease, 163 (47 per cent) had a history of hypertension and 40 (11 per cent) were diabetic.

Relation between carotid plaque characteristics and symptoms

Distribution of plaque types and surfaces were as follows: type I, 91 (26 per cent), type II, 173 (50 per cent); type III, 46 (13 per cent); type IV, 40 (11 per cent); smooth, 118 (34 per cent); irregular, 156 (44 per cent); ulcerated, 76 (22 per cent). *Figs 2* and *3* illustrate the distribution of plaque types and surface in relation to presenting symptom. Plaque types I and II were more common in symptomatic than asymptomatic patients (83 *versus* 44 per cent; $\chi^2 = 52{\cdot}6$, 3 d.f., $P < 0{\cdot}0001$ on univariate analysis). Ulceration was also more common in symptomatic patients (23 *versus* 14 per cent, $\chi^2 = 6{\cdot}1$, 2 d.f., $P = 0{\cdot}04$ on univariate analysis).

In symptomatic patients there was no association between type of presenting symptom and plaque morphology or surface features ($\chi^2 = 10{\cdot}3$, 18 d.f., $P = 0{\cdot}9$; $\chi^2 = 7{\cdot}9$, 12 d.f., $P = 0{\cdot}8$ on univariate analysis). On multivariate analysis plaque morphology held its association with the presence of symptoms (regression coefficient 0·23, $t = 4{\cdot}4$, $P < 0{\cdot}0001$) but surface ulceration (regression coefficient 0·135, $t = 1{\cdot}6$, $P = 0{\cdot}1$) and degree of carotid stenosis (regression coefficient 0·09, $t = 1{\cdot}8$, $P = 0{\cdot}1$) were not significantly related to symptoms.

Table 1 Multivariate regression analysis

	Regression coefficient	*t*	*P*
Plaque morphology	−0·151	2·7	0·008
Age	−0·1	1·6	0·1
Common carotid stenosis	0·05	1·0	0·3
Plaque ulceration	0·08	0·9	0·4
Internal carotid stenosis	0·04	0·7	0·5
Sex	−0·025	0·5	0·6
Plaque surface	0·006	0·07	0·9

The effect of independent variables is listed in determining separation of patients into asymptomatic, non-stroke symptoms, stroke with warning and stroke without warning groups. No variable predicted separation of patients suffering stroke without warning from all other patients

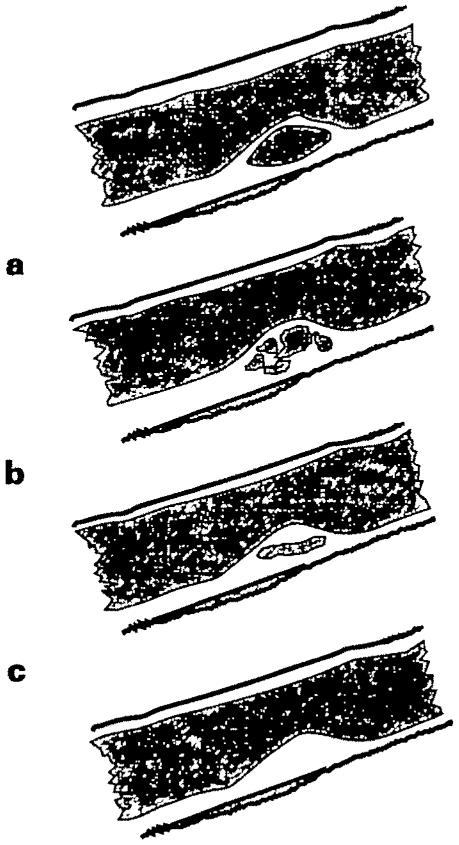

Fig. 1 Gray-Weale classification of carotid plaque types. **a** Type I, echolucent plaques with a thin echogenic cap; **b** type II, substantially echolucent plaques with small areas of echogenicity; **c** type III, dominantly echogenic lesions with small areas of echolucency (less than 25 per cent), **d** type IV, uniformly echogenic lesions (equivalent to homogeneous)

Relation between plaque characteristics and history of stroke without warning

To seek an association between plaque characteristics and stroke without warning, all the patients on the database were separated into four groups: asymptomatic ($n = 65$), patients who presented with a transient neurological event ($n = 204$), stroke with warning ($n = 5$) and stroke without warning ($n = 76$). On multivariate analysis there was an association between the type of presentation and plaque morphology (*Table 1*). However, if either the asympto-

Table 2 Plaque morphology and patient characteristics

	Carotid plaque morphology			
	Type I	Type II	Type III	Type IV
Median age (range) years	68 (40–82)	68 (38–90)	69 (54–78)	68 (47–89)
Men (%)	78	71	55	61
Ischaemic heart disease (%)	25	37	45	39
Peripheral vascular disease (%)	36	39	27	43
Hypertension (%)	66	43	36	46
Diabetes mellitus (%)	10	14	9	7
Mean(s.d.) internal carotid stenosis (%)	78(20)	82(15)	68(7)	77(24)
Surface ulceration (%)	26	26	5	14

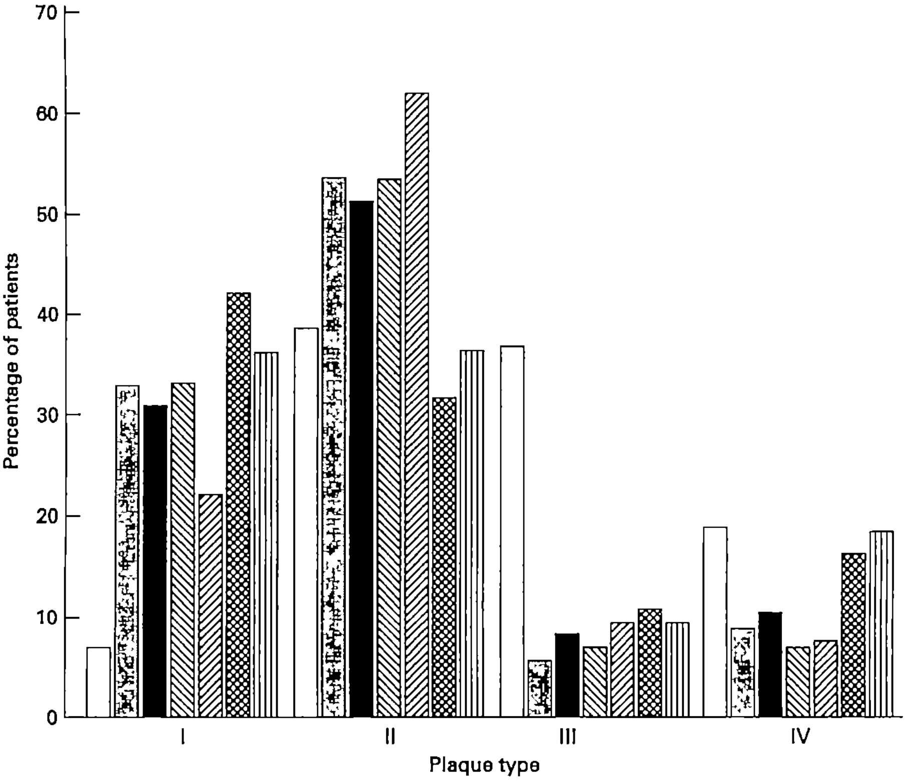

Fig. 2 Plaque type related to presenting symptom. □, Asymptomatic ($n = 65$); □, amaurosis fugax ($n = 58$); ■, transient ischaemic attack (TIA) ($n = 127$), ▨, transient stroke ($n = 15$), ▨, established stroke ($n = 55$); ▩, crescendo TIA ($n = 19$); □, progressive stroke ($n = 11$)

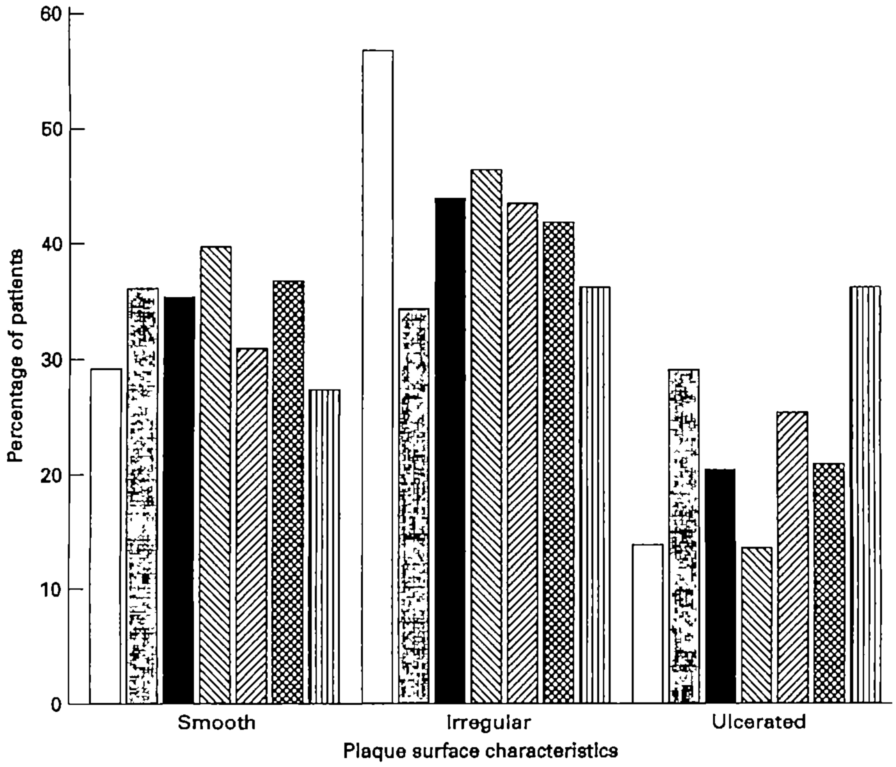

Fig. 3 Plaque surface characteristics related to presenting symptom □, Asymptomatic ($n = 65$); □, amaurosis fugax ($n = 58$); ■, transient ischaemic attack (TIA) ($n = 127$); ▨, transient stroke ($n = 15$); ▨, established stroke ($n = 55$); ▩, crescendo TIA ($n = 19$); □, progressive stroke ($n = 11$)

matic patients were excluded or patients were simply separated into those suffering stroke without warning ($n = 76$) and other symptomatic or asymptomatic patients ($n = 274$) none of the variables examined remained significant.

Factors related to plaque morphology

Table 2 illustrates patient variables in relation to plaque morphology. The only characteristic to have a significant association was surface ulceration (regression coefficient 0·843, $t = 4$, $P < 0{\cdot}0001$); 26 per cent of type I and II plaques compared with 10 per cent of type III and IV plaques had ulceration. Degree of internal carotid stenosis was unrelated to plaque morphology (*Table 2*); however, all patients in this study had 60–99 per cent stenosis.

Discussion

The North American Symptomatic Carotid Endarterectomy Trial (NASCET) demonstrated that the annual stroke rate for patients with a symptomatic 70–99 per cent carotid stenosis was 13 per cent[1], whereas the American asymptomatic trial found that the annual stroke rate for patients with asymptomatic 60–99 per cent carotid stenosis was only 2 per cent[16]. The NASCET study also emphasized that different cerebral symptoms may be associated with different prognoses. In a subset of patients with 70–99 per cent internal carotid stenosis in the medical arm of the trial, the cumulative stroke rate at 24 months for those who presented with amaurosis fugax was 17 per cent compared with 44 per cent for those who presented with a TIA ($P = 0{\cdot}005$)[17]. In this study a cross-sectional analysis has been performed in an attempt to identify features associated with different presentations of carotid artery disease. Plaque morphology was examined since previous studies have suggested that this feature may be predictive[8–10].

A number of different classifications of the ultrasonographic appearance of carotid plaques have been published based on the echogenicity of the lesion. The simplest is to describe plaques as homogeneous (echogenic) or heterogeneous (mixed)[8,9]. The classification used in the present study is based on that of Gray-Weale *et al.*[15]. Type I plaques are predominantly echolucent, type II echolucent with areas of echogenicity, type III echogenic with areas of echolucency and type IV predominantly echogenic (*Fig. 1*).

In this study a significant association was demonstrated between the presence of cerebrovascular symptoms and carotid plaque morphology in patients with a similar degree of carotid stenosis. Plaque types I and II were twice as common in symptomatic patients. While surface ulceration was more common in symptomatic patients, the association did not reach statistical significance on multiple regression analysis This finding can be explained by the positive association between ulceration and type I and II plaques (*Table 2*).

This relationship between plaque morphology and presence of symptoms is in agreement with previous cross-sectional studies[8–10]. For example, Langsfeld *et al.*[10] compared plaque types in 252 symptomatic and 260 asymptomatic patients and discovered a significantly greater number of plaque types I and II in symptomatic patients. Similarly, others have found the presence of surface ulceration to be less predictive[18,19]. Few longitudinal studies have examined the role of plaque morphology in identifying which asymptomatic patients are likely to develop symptoms. Those performed have suggested an association between type I and II plaques and the subsequent development of neurological symptoms[20,21]; however, larger studies are required to confirm this.

It has been suggested that the type of carotid plaque may determine the type of cerebral emboli and therefore the form of presentation[11]. Grigg *et al.*[11] studied the computed tomographic brain scans of 70 patients with amaurosis fugax and 104 patients with TIA and related the degree of internal carotid stenosis to the incidence of atrophy and cerebral infarction. In patients with amaurosis fugax the incidence of both infarction and atrophy increased with the degree of internal carotid stenosis, whereas in patients with a TIA the incidence of infarction, but not atrophy, increased with the degree of internal carotid stenosis. On the basis of these findings it was postulated that patients with amaurosis fugax were suffering showers of small emboli resulting in silent cerebral infarcts until an embolus lodged in a branch of the ophthalmic artery. In contrast, patients with TIAs suffered larger emboli and therefore presented earlier before atrophy could develop.

While it is useful to be able to predict patients likely to develop symptoms from their carotid stenosis it is more important to be able to identify patients likely to suffer stroke without warning. Following from the suggestions of Grigg *et al.*[11] it was hoped that plaque morphology might be predictive of patients presenting with stroke without warning. However, none of the features examined in this study were predictive of stroke without warning. The reason for this is the lack of association between plaque morphology and type of presenting symptom (*Fig. 2*). Thus while plaque morphology was different in asymptomatic patients compared with those who have had any symptom related to the carotid artery, it was not useful in predicting whether this was a TIA or a stroke without warning.

Plaque morphology may be different in asymptomatic and symptomatic patients with similar degrees of carotid stenosis. However, this study provides no evidence to suggest that plaque morphology will be useful in identifying patients who develop a stroke without warning.

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Predicting changes in the distribution of sweating following thoracoscopic sympathectomy

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Background Compensatory sweating is a common symptom following thoracic sympathectomy; however, the reported incidence of this complication varies greatly, and its severity has not been quantified.

Methods In this study changes in the distribution of sweating following bilateral T2–3 thoracoscopic sympathectomy for hyperhidrosis were assessed in 42 patients. Sweat production in the palms, axillae, face, trunk and feet was assessed using a linear analogue scale.

Results The operation was most successful in reducing sweat production in the palms, axillae and face (in descending order). The operation also reduced pedal sweat production in 12 of the 29 patients who suffered concomitant pedal hyperhidrosis. Compensatory truncal sweating occurred in 36 of the 42 patients; it was severe in ten, moderate in 16 and minimal in ten.

Conclusion Patients should be warned about compensatory sweating before thoracic sympathectomy.

Sympathectomy is currently the most acceptable surgical treatment for disabling upper limb hyperhidrosis. The incidence of palmar hyperhidrosis may be as high as 1 per cent[1] and a positive family history can be obtained in 30–50 per cent of cases. Hyperhidrosis affects the skin of the whole body but its clinical effects are seen in areas with a high density of eccrine sweat glands (palms, axillae and soles)[2,3].

The primary surgical treatment is to divide, or ablate with diathermy, the second, third and possibly the fourth thoracic sympathetic ganglia. The approach may either be supraclavicular[4] or transaxillary using an open or endoscopic technique[5]. The results of a successful thoracic sympathectomy are predictable with the hands being rendered completely anhydrotic and the axillae being dried by a factor of 80 per cent. The effects of sympathectomy appear to be permanent.

The complications of thoracoscopic sympathectomy include compensatory sweating, gustatory sweating, phantom sweating, a transient increase in upper limb sweating, facial anhydrosis, ptosis, meiosis, excessively dry skin of the hands and recurrence of hyperhidrosis. Pulmonary complications include dyspnoea, pneumothorax, haemothorax and pleural effusion. Two cases of intraoperative cardiac arrest have also been reported during thoracoscopic sympathectomy[6].

Compensatory sweating is one of the most troublesome and commonly noted complications. The reported incidence of compensatory sweating following thoracic sympathectomy varies from 24 to 81 per cent[7,8] but few reports mention its distribution and severity. In this study the changes in distribution and extent of sweating following a T2–3 thoracoscopic sympathectomy were defined with the aim of investigating which, if any, factors could predict the occurrence of postoperative compensatory sweating.

Patients and methods

Forty-two consecutive patients (28 women, 14 men) undergoing a T2–3 thoracoscopic sympathectomy for primary hyperhidrosis were included in the study. The mean(s.d.) age of the patients was 32(10) years and the mean age at onset of symptoms was 11(8) years. Thirty-four patients suffered hyperhidrosis affecting the hands, the axillae were affected in 28 patients, and the face in 11. Pedal hyperhidrosis affected 29 patients. In all cases hyperhidrosis was bilateral. Although the operation was usually performed to treat hyperhidrosis of the hands and axillae, in eight patients the hands were not involved and it was done to treat hyperhidrosis affecting either the face and/or axilla. Nine subjects had a family history of hyperhidrosis.

A preoperative chest radiograph was taken to identify any pulmonary pathology that may cause pleural adhesions. Under a general anaesthetic a T2–3 thoracoscopic sympathectomy was performed using the method described previously[9].

To quantify the amount of sweating at various sites (hands, axillae, face, feet and trunk) before and after the operation, patients were asked to complete a linear analogue scale. The scale ranged from 0 to 10; a score of 0 indicated no sweating at rest, and a score of 10 indicated visible sweat droplets at rest.

Mean(s.d.) follow-up was 11(17) months. Student's t test was used for the statistical analysis.

Results

The overall results of the operation can be seen by comparing the amount of sweating at a particular site before operation with that following surgery (*Fig. 1*). Palmar hyperhidrosis was reduced from a mean score of 7·1 before operation to 0·4 after sympathectomy ($P<0·001$); for the axillae the scores were 6·1 and 2·3 respectively ($P<0·001$) and for the face 2·6 to 1·5 ($P=0·054$). Interestingly a small reduction in pedal sweating was also noted from a preoperative score of 6·3 to 5·1 after operation ($P=0·032$). The principal complication of the operation was compensatory sweating affecting the trunk. Truncal sweat production increased from a mean preoperative score of 1·7 to a postoperative score of 5·4 ($P<0·001$).

To demonstrate the effect of the operation on sweating at a particular site, the scored amount of sweating at that site after operation was subtracted from the preoperative score, to give the sweat score. The sweat score measured the perceived change in sweat production at a particular site following surgery. It quantifies both the efficacy of surgery, and the severity of complications (compensatory

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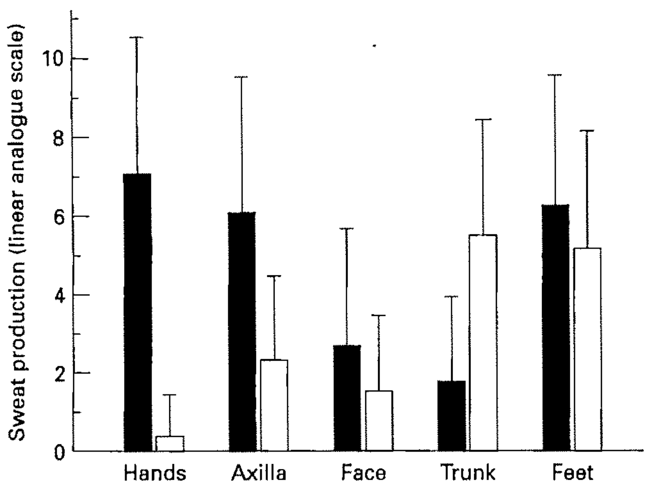

Fig. 1 Sweat production at different sites before (■) and after (□) T2–3 thoracoscopic sympathectomy. Values are mean(s.d.) score on a linear analogue scale

sweating, gustatory sweating and facial anhydrosis). On a scale of +10 to −10, the higher the positive sweat score the drier the area and the higher the negative sweat score the wetter the area; a sweat score of zero indicates that the operation had no effect on sweat production at that site.

Palmar sweating

Hyperhidrosis of the palms affected 34 patients; the operation produced a good result in 32 and a moderate result in two patients. Those without palmar hyperhidrosis before operation noticed little or no change in palmar sweat production.

Axillary sweating

Twenty-eight patients had axillary hyperhidrosis. The operation produced a good result in 14, a moderate result in eight and a poor result in five; one patient was worse following surgery. The operation had no effect on axillary sweating in patients who had not complained of preoperative axillary hyperhidrosis.

Facial sweating

The 11 patients who had excessive preoperative facial sweating were all helped by the operation. The result could be classified as good in five and moderate in six. Of the 31 patients with normal preoperative facial sweating two noticed significant facial anhydrosis, and ten gustatory sweating which was severe in two patients (*Fig. 2*).

Pedal sweating

Twenty-nine patients complained of preoperative pedal hyperhidrosis; five had a marked improvement in their symptoms whilst seven had a moderate improvement. In 17 patients the operation had little or no effect. Of the 13 patients with normal preoperative plantar sweating five noticed an increase in plantar sweating which was severe in one.

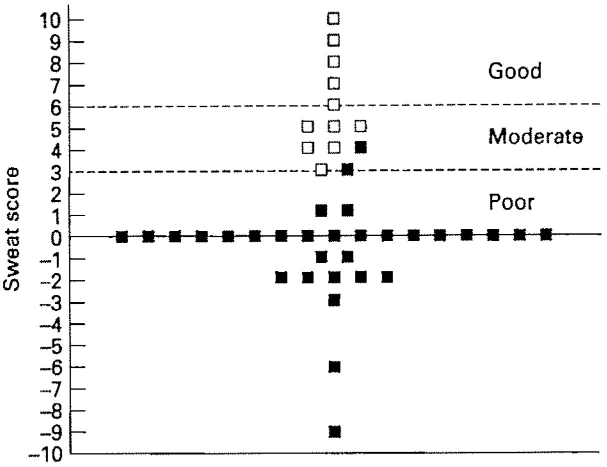

Fig. 2 Change in facial sweating caused by sympathectomy, expressed as sweat scores (rounded to the nearest whole number: −10 to −1, gustatory sweating; 1 to 10, facial anhydrosis), in patients with preoperative facial hyperhidrosis (□) and patients with normal preoperative facial sweating (■) Good, 6 to 10; moderate, 3 to 6, poor, 0 to 3

Truncal sweating

Only one patient complained of preoperative truncal hyperhidrosis and he noticed a marginal improvement in his symptoms after operation. Compensatory sweating affected 36 of the 42 patients after sympathectomy and was severe in ten, moderate in 16 and minimal in ten.

Discussion

The greatest change in sweating after sympathectomy was noticed in the hands. The results for axillary hyperhidrosis were not as impressive; five of 28 patients with preoperative axillary hyperhidrosis had a poor result. It has been suggested that a more extensive sympathectomy (T2–6) should be performed if axillary hyperhidrosis is to be treated[10], but this might increase compensatory sweating.

Gustatory sweating may become excessive after thoracic sympathectomy. This has been attributed to aberrant regeneration of sympathetic nerves[11], but increased activity or budding of intact sudomotor fibres might be an alternative explanation. In this series gustatory sweating affected ten of 31 patients with normal preoperative facial sweating.

Compensatory sweating may affect the abdomen, back, thighs, feet and face. Most patients conclude that compensatory sweating is preferable to palmar hyperhidrosis. The mechanism of compensatory sweating remains poorly understood. Compensatory sweating appears to be a generalized phenomenon affecting any sweat glands that remain innervated. Following a bilateral T2–3 sympathectomy approximately 40 per cent of the body's sweat function is lost, and truncal hyperhidrosis is a compensatory mechanism of thermoregulation[12]. Compensatory sweating tends to increase in response to an increase in temperature.

Excessive truncal compensatory sweating is worst in patients who have bilateral thoracic and lumbar sympathectomies. Hederman[7] reported that upper limb sympathectomy could be achieved by excision of the second thoracic ganglion only, with a reduced incidence of compensatory sweating (64 per cent following T2–4 sympathectomy reduced to 24 per cent by isolated excision of the T2 ganglion). Hsu *et al.*[8] and Kao and co-workers[13] however, reported the incidence of compensatory sweating as 81 and 66 per cent respectively following T2 sympathectomy.

The concentration of sweat glands on abdominal skin is variable[14] and the extent to which these glands are stimulated depends both on the maintenance of thermoregulation and on emotional sympathetic activity. Emotional stimulus increases sweat production proportionately over the whole body[2]. For these reasons it is difficult to predict accurately which patients will suffer from severe compensatory sweating after operation. In this study, although most patients (36 of 42) suffered from truncal compensatory sweating, it was severe in ten. Patients should be warned about compensatory sweating before thoracic sympathectomy.

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Twelve-year experience of the management of ruptured abdominal aortic aneurysm

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Background The operative mortality rate for elective repair of asymptomatic abdominal aortic aneurysm (AAA) is falling but the fate of patients with ruptured AAA may have changed little over the past decade.

Methods This study was an analysis of a prospectively gathered computerized database.

Results In the 12 years to 31 December 1994, 1144 patients underwent (attempted) repair of AAA. In 514 patients (44·9 per cent) who had an operation for ruptured AAA there was no significant change in the mean age, male:female ratio (418:96) or operative mortality rate (35·0 per cent) over the interval of the study. Forty-seven patients died before reaching the operating theatre, giving an 'intention to operate' mortality rate of 40·5 per cent. A further 68 patients (10·8 per cent of all patients who presented with a ruptured AAA) were not offered operation because of poor medical condition ($n = 34$) or extreme age ($n = 34$); three patients refused operation. A greater proportion of patients had surgery between 1989 and 1994 (276 of 323, 85·4 per cent) than between 1983 and 1988 (238 of 309, 77·0 per cent) ($P < 0·01$, χ^2 test).

Conclusion The proportion of aneurysms operated on for rupture in this unit remains high (almost 50 per cent). The results of surgery for ruptured AAA have not improved in the past 12 years.

Results from specialist centres indicate that the operative mortality rate following elective repair of asymptomatic abdominal aortic aneurysm (AAA) is falling, although this may not be the true situation in most hospitals[1,2]. By contrast, the operative mortality rate for repair of ruptured AAA may have changed little over the past decade[3]. The aim of the present study was to review the results of surgery for ruptured AAA over 12 years from 1 January 1983 (the first year of the Edinburgh Regional Vascular Unit) to 31 December 1994. Since a proportion of patients who present with ruptured AAA do not undergo operation and because the selection of patients for operation clearly affects overall outcome, the characteristics of the non-operated group were also examined.

Patients and methods

Data gathered prospectively from the Lothian Surgical Audit on all patients admitted to the Edinburgh Regional Vascular Unit with a diagnosis of AAA have been analysed. This unit receives all vascular surgery patients for the City of Edinburgh and acts as a tertiary referral centre for the South-East of Scotland (total population approximately 1·2 million). The catchment area extends for 50 miles south into the Borders, 25 miles north into Fife and 20 miles west towards Glasgow; total area approximately 4500 square miles. Operative death has been defined as death within 30 days of surgery or during the same admission as the first operation. A patient was classified as having had an AAA operation if an anaesthetic was given with the intention of repairing the aneurysm regardless of whether a graft was successfully inserted. Rupture was defined as the presence of retroperitoneal and/or intraperitoneal blood in the absence of any other identifiable cause for haematoma other than an aneurysm. Patients who had a suspected ruptured AAA but at operation were found to have other pathology, or no haematoma associated with their aneurysm, were excluded from the analysis.

Results

Operated patients

A total of 1144 patients underwent operation for AAA; 352 (30·8 per cent) were asymptomatic, 278 (24·3 per cent) were symptomatic and 514 (44·9 per cent) had a ruptured aneurysm. During the same interval, a further 118 patients with a ruptured AAA did not have surgery (*Fig. 1*). In patients with a ruptured AAA, there was no significant alteration in the mean age, male:female ratio

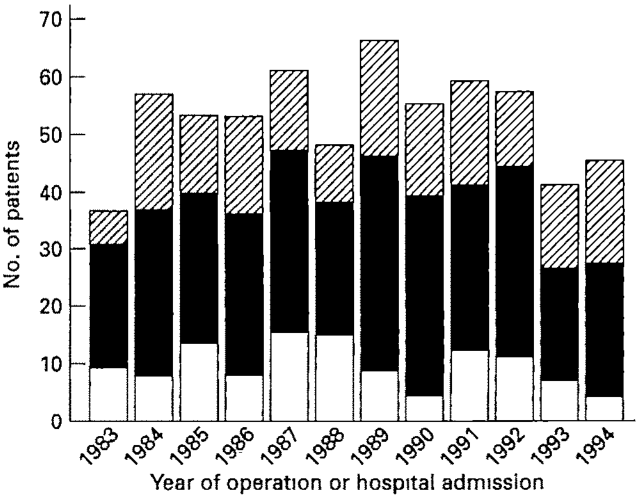

Fig. 1 All patients with ruptured abdominal aortic aneurysm 1983–1994. ☐, Not operated; ■, survived operation; ▨, died following operation

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(418:96), or operative mortality rate over the interval of the study. Between 1983 and 1988, 80 of 238 operated patients (33·6 per cent) died, compared with 100 of 276 (36·2 per cent) between 1989 and 1994 (χ^2 with Yates' correction 0·28, $P = 0{\cdot}6$). Some 180 patients (35·0 per cent) died within 30 days of operation or during the same admission; 146 were men (median age 72·1 years) and 34 were women (median age 74·8 years). Seventy-seven died during surgery and 103 after the operation was completed. There was no significant difference between the median age of survivors (76·2 years) and non-survivors (72·6 years). Of 48 patients aged 80 years or older, 21 died within 30 days of surgery, compared with 159 (34 per cent) of 466 patients aged under 80 years (χ^2 with Yates' correction 1·38, $P = 0{\cdot}24$). There was no significant difference in mortality rate between patients who received bifurcated grafts (66 of 216) and those who received straight grafts (67 of 251). Forty-seven patients had no graft inserted at operation and all died in theatre. As a proportion of the total number of operations there were significantly more straight grafts inserted between 1989 and 1994 (170 of 276) than between 1983 and 1988 (81 of 238) (χ^2 with Yates' correction 48·03, $P < 0{\cdot}0001$)[4].

Non-operated patients

Overall, 118 patients (18·7 per cent of all patients with ruptured AAA) were admitted with ruptured AAA but did not undergo surgery. There were 69 men (median age 73 (range 54–93) years) who were significantly younger than the 49 women (median age 81 (range 63–93) years) ($P < 0{\cdot}01$, Mann–Whitney *U* test). Non-operated patients were significantly more likely to be women: 96 of 514 operated *versus* 49 of 118 non-operated (χ^2 with Yates' correction 27·6, $P < 0{\cdot}0001$). The proportion of patients who did not have surgery was significantly less between 1989 and 1994 (47 of 323, 14·6 per cent) than between 1983 and 1988 (71 of 309, 23·0 per cent) (χ^2 with Yates' correction 6·84, $P < 0{\cdot}01$).

In 47 patients (35 men, mean age 74 years and 12 women, mean age 76 years) the decision to operate had been made but the patient died from shock or cardiac arrest in the emergency room, *en route* to the operating theatre, or in the anaesthetic room. Accurate data are not available on the delay between onset of symptoms, correct diagnosis and access to an operating theatre. However, most patients arrive in this unit within 1–2 h of being accepted for transfer. No clinically or statistically significant difference in outcome was identified between patients admitted directly to the Edinburgh Royal Infirmary and those transferred from other hospitals, but this is an area of ongoing research.

In a further 71 patients an active decision was made not to operate. This decision was reached after discussion between the duty anaesthetist and surgeon, both of whom had seen and discussed the patient with their respective consultant and/or senior registrar. The views of the patient, if still conscious, were properly taken into account and the relatives were involved if appropriate. It is recognized that in most cases several factors are taken into account when deciding not to operate on a patient with ruptured AAA; the predominant reasons are shown in *Table 1*. In 34 instances the decision was influenced primarily by age, although the majority of these patients were shocked and had co-morbidity. In this group there were 16 men (mean age 86 (range 82–93) years) and 18 women (mean age 87 (range 81–92) years). In a further 34 instances the decision not to operate was made primarily on the basis of poor general medical condition. Ten patients known to have an AAA had been deemed unfit for elective repair by a consultant anaesthetist attached to the Vascular Surgery Unit. After full discussion of the risks and benefits, three patients aged 80, 81 and 83 years respectively declined the offer of operation.

Table 1 Reasons for patients with ruptured abdominal aortic aneurysm not having surgery

Reason	No. of patients
Patient died before reaching operating theatre	47
Patient deemed unsuitable primarily on basis of extreme age	34
Patient deemed unfit for operation primarily because of:	
Ischaemic heart disease	10
Chronic obstructive airway disease	8
Co-existent malignancy	3
Parkinson's disease	1
Dementia	2
Chronic renal failure	3
Previous stroke	4
Known thoracoabdominal extension of aneurysm	2
Co-existent severe acute pancreatitis	1
Patient declined surgery	3

Discussion

The present study provides details of catchment area, referral practices, selection policies, as well as the clinical status of patients who did not have surgery for ruptured AAA. This unit provides the only 24-h, 365-day emergency vascular surgery service in south-east Scotland (population approximately 1·2 million) and the results represent the total referred ruptured AAA experience for this defined geographical area over 12 years. This service is provided by three consultants; two higher and two basic surgical trainees; and four preregistration house officers. Two research fellows also take part in the emergency rota. The study does not include patients who died at home or in hospital with undiagnosed ruptured AAA; nor patients in whom the diagnosis was made locally but who, for various reasons, were not referred or transferred to this unit. Operated patients had a 35·0 per cent perioperative mortality rate. A further 47 patients died before operative repair could be done giving an 'intention to operate' mortality rate of 40·5 per cent (227 of 561). These results are comparable to other published values[3,5–11].

Mortality figures for ruptured AAA vary considerably depending on the chosen denominator[12]. For example, in the present study, if all patients who presented with ruptured AAA are considered, the mortality rate was 47·2 per cent. If only those in whom a positive decision to operate was made are included then the 'intention to operate' mortality rate was 40·6 per cent. The mortality rate in patients who had surgery was 35·0 per cent. The 'intention to operate' mortality rate is perhaps the most revealing as it reflects not only surgical and anaesthetic expertise, but also the effectiveness of diagnosis, resuscitation and transfer.

Whether to subject an elderly patient with significant co-morbidity to emergency repair of a ruptured AAA is a difficult decision[13–16]. It has been stated that only a minority of these patients survive operation and their subsequent quality of life may be poor[17,18]. The resource implications of using the intensive therapy unit for these patients will inevitably come under scrutiny[19]. Despite these concerns, a significantly higher proportion of patients had surgery in the latter half of the study. This may reflect a growing expectation from referring hospitals, relatives and perhaps patients that operative intervention for ruptured AAA should be considered regardless of age and frailty. Some vascular surgeons still believe that every patient with a ruptured aneurysm should be offered surgery. Such an approach cannot be justified on either humane or medical grounds. Present data support the contention that in carefully selected octogenarians the results of operative repair are satisfactory.

Although these data do, at least in part, reflect a worsening 'case mix', there was no improvement in the results of surgery for ruptured AAA over the past 12 years, despite surgical and anaesthetic subspecialization. In addition, it is disappointing that, despite an increasing awareness of the condition and more liberal use of ultrasonography, almost 50 per cent of all AAA repairs are still performed for rupture[20]. There is little prospect of improving current results significantly and the only prospect of reducing the mortality and morbidity rates from AAA is to detect and repair more aneurysms before rupture. The debate on population screening continues unresolved.

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Supervised training in carotid endarterectomy is safe

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Background The number of carotid endarterectomies (CEAs) performed in the UK, and thus the need to train surgeons in this operation, has increased markedly in recent years and may continue to do so. The aim of the present study was to assess the quality, clinical outcome and case-mix of supervised training in CEA in this unit.

Methods The study was an analysis of a prospectively gathered database of all CEAs performed in this unit since 1975.

Results Between 1 January 1975 and 31 December 1991, 247 CEAs were performed of which only 12 were done by supervised trainees. By contrast, between 1 January 1992 and 1 July 1996, 219 CEAs were performed, 92 (42 per cent) by supervised trainees ($P < 0.0001$). In cases performed since 1 January 1992, there was no significant difference between trainee and consultant operations with regard to age and sex of patient, smoking history, ischaemic heart disease, hypertension, diabetes, presence of preoperative infarction on computed tomography, indications for operation, degree of ipsilateral carotid stenosis, status of the contralateral carotid artery, use of a shunt or patch angioplasty. Since 1 January 1992, the total perioperative neurological event rate for supervised trainees was seven of 92 (7·6 per cent) of which one was fatal (cerebral infarction). The total neurological event rate for operations done by a consultant was nine of 127 (7·1 per cent), of which one was permanent and disabling and two were fatal (one cerebral infarction and one haemorrhage).

Conclusion Since 1991 there has been a tenfold increase in the proportion of CEAs being performed by supervised trainees. This has been accomplished without deterioration in clinical outcome. With adequate supervision, training in CEA can be safe, even when trainees are exposed to a true cross-section of low-, medium- and high-risk cases.

The number of carotid endarterectomies (CEAs) performed in the UK has increased markedly in recent years[1]. This has occurred particularly since two large, multicentre, randomized controlled trials confirmed that CEA, in addition to best medical therapy, significantly reduced ipsilateral stroke in patients with symptomatic carotid stenosis in excess of 70 per cent, when compared with best medical treatment alone[2–4]. More recently, the Asymptomatic Carotid Atherosclerosis Study has reported benefit from CEA in asymptomatic patients with stenosis in excess of 60 per cent[5] and the Asymptomatic Carotid Surgery Trial is to report soon[6]. As a consequence of these developments, the demand for CEA will continue to increase as, of course, will the need for adequately trained surgeons to undertake the procedure. The aim of this present study was to assess the changes in training in CEA that have occurred in this unit in recent years. In particular, the risk factors and clinical outcome of patients operated on by trainees were compared with those of patients operated on by a consultant.

Patients and methods

A prospectively gathered database of all CEAs performed in this unit since 1975 was interrogated. This database recorded the demographic details of the patient, indications for operation, the surgeon and assistant at the operation; the results of investigations such as angiography and computed tomography (CT); the anaesthetic given; operative details such as the use of a shunt or a patch angioplasty technique; and clinical outcome.

Results

Between 1 January 1975 and 31 December 1991, 247 CEAs were performed of which only 12 (4·9 per cent) were done by supervised trainees. By contrast, between 1 January 1992 and 1 July 1996, 219 CEAs were performed, 92 (42 per cent) by supervised trainees ($P < 0.0001$, Fisher's exact test) (*Fig. 1*). All operations were performed under general anaesthesia and under direct consultant supervision; that is, the consultant was scrubbed at the operating table for all or part of the operation, and was immediately available in the operating suite during the part of the operation where he was not scrubbed. In patients operated on since 1 January 1992, there were no significant differences with regard to age and sex of patients treated by trainee (median age 64 (range 42–85) years; 63 men, 29 women) or consultant (median age 65 (range 38–72) years; 71 men, 56 women). There was also no significant difference with regard to clinical or operative details (*Table 1*) or CT. The total perioperative neurological event rate for supervised trainees was seven of 92 (7·6 per cent); of which six resolved during the same hospital admission and one was fatal (cerebral infarction). By comparison, the total neurological event rate for consultant operations was nine of 127 (7·1 per cent); of which six resolved during the same hospital admission, and three were permanent and disabling. Two of these three patients died; one from cerebral infarction and one from cerebral haemorrhage (*Table 2*).

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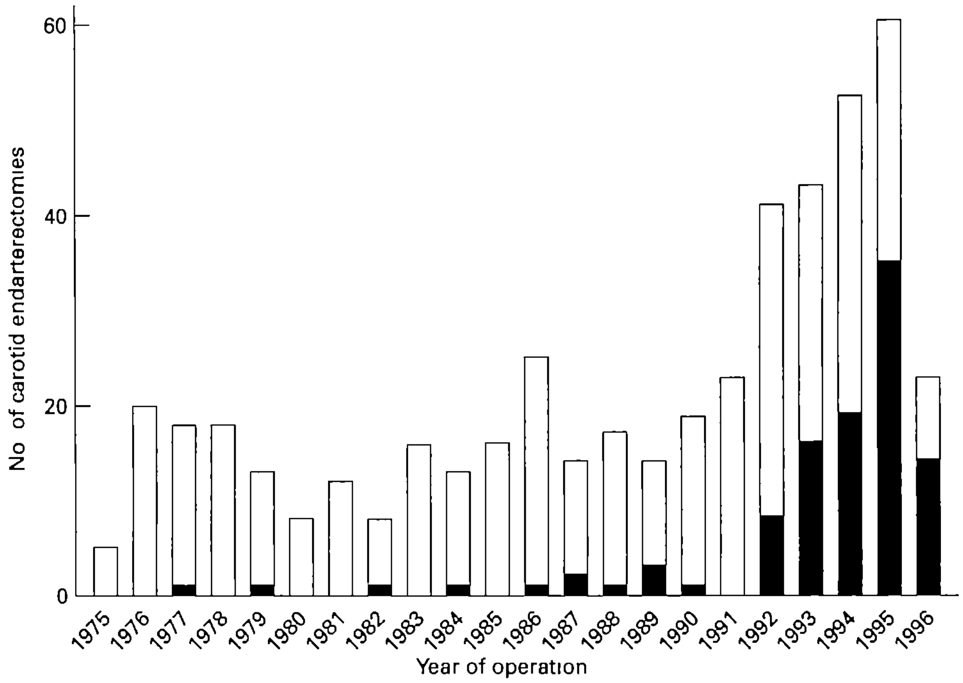

Fig. 1 Carotid endarterectomy (CEA) performed by surgeons in training (■) and consultants (□) per year between 1 January 1975 and 1 July 1996

Discussion

In a previous study of 82 consecutive patients undergoing 101 consecutive CEAs performed by fourth and fifth year general surgical residents under direct staff supervision, the operative stroke rate was 3 per cent and the mortality rate 1 per cent. The authors concluded that their trainees' results did not compromise patient care[7]. Archie[8] analysed a personal series of 600 consecutive primary CEAs, performed over 13 years, beginning as a senior resident. The mortality rate was 1·5 per cent and the permanent neurological morbidity rate was 3·3 per cent. Morbidity and mortality rates both decreased with cumulative experience although this trend did not attain statistical significance. Bloom *et al.*[9] studied 129 patients undergoing 153 CEAs from 1980 onwards, of which 93 per cent were performed by the chief medical resident under direct supervision. In this group there were no deaths and a morbidity rate of 1·3 per cent. Krupski *et al.*[10] studied 300 patients undergoing CEA; 200 by an experienced vascular surgeon and 100 by general surgical senior residents under direct supervision in a Veterans Administration (VA) hospital. Despite VA patients having more severe arterial disease, there was no increase in morbidity or mortality rate in this group, although CEA performed by residents took significantly longer. Hertzer *et al.*[11] examined the morbidity and mortality rates (2·4 and 1·2 per cent respectively) following 2646 CEAs performed over 3 years and found that outcome was not significantly influenced by the size of the 27 participating hospitals, nor

Table 1 Comparison of carotid endarterectomy performed by surgeons in training and consultants between 1 January 1992 and 1 July 1996

	Surgeon in training ($n = 92$)	Consultant ($n = 127$)
Indications for operation*		
Asymptomatic	4	6
Amaurosis fugax	31	27
Retinal artery occlusion	5	4
Transient ischaemic attack	53	73
Stroke with recovery	12	17
Stroke with residual deficit	23	20
Co-morbidity and risk factors		
Current smoker	31	54
Angina	22	35
Previous myocardial infarction	19	25
Diabetic	11	19
Hypertension	45	77
Intermittent claudication	21	33
Investigations		
CT performed	47	54
CT showed infarction	25	25
Contralateral occlusion	8	11
Operative details		
Shunt used	35	53
Patch angioplasty	83	97

*There may be more than one indication per patient. CT, computed tomography

Table 2 Results of carotid endarterectomy performed by surgeons in training and consultants between 1 January 1992 and 1 July 1996

	Surgeon in training ($n = 92$)	Consultant ($n = 127$)
Cranial nerve deficits and haematoma	14	18
Intraoperative stroke		
Without residual deficit	4	3
With residual deficit	0	1
Postoperative stroke		
Without residual deficit	2	3
With residual deficit	0	0
Fatal	1	2

the annual experience of the 29 surgeons. Dalsing[12] examined 100 CEAs performed by training surgeons under his supervision. There was no death, one transient and one permanent neurological complication, and four neck haematomas which required evacuation.

The benefits of CEA, over best medical treatment alone, depend crucially on the operation being undertaken with minimum morbidity and mortality rates. In the randomized controlled trials cited above, operations were performed in centres with proven experience and, presumably, in the majority of cases, by experienced vascular surgeons. If the good reputation of CEA is to be maintained, a new generation of vascular surgeons capable of emulating, and hopefully improving on these results is needed. Since 1 January 1992, there has been a tenfold increase in the proportion of CEAs performed by supervised trainees in this unit without any deterioration in clinical outcome. In particular this was accomplished without 'protecting' trainees from a true cross-section of the population at risk. A growing proportion of patients who undergo CEA are high risk with a preoperative neurological deficit or severe ipsilateral and contralateral carotid disease[4]. It is important, therefore, that trainees be exposed to these patients so they become fully acquainted with placement of shunts and the use of patch angioplasty where appropriate. The present study indicates that vascular trainees can be trained adequately and safely in CEA, given appropriate supervision from experienced consultant staff.

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Management of chylothorax

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Background Chylothorax is a rare primary or secondary condition the optimum management of which remains uncertain.

Methods Twenty cases of chylothorax, including ten of primary chylothorax and ten secondary to either malignancy, subclavian vein thrombosis or lymphangioma treated between 1956 and 1986 have been reviewed.

Results Open pleurectomy was the most successful treatment in preventing reaccumulation of the effusion. Three patients had thoracic duct–azygous vein anastomoses, but all anastomoses were probably occluded within a year of surgery. Three patients have been lost to follow-up and five died within 2 years of their treatment, but 12 patients were alive and free from an effusion 3–22 years after treatment.

Conclusion Patients with chylothorax should undergo lymphangiography to identify the cause and site of the lymphatic abnormality. Conservative treatment is successful in some patients but should be abandoned if the fluid loss exceeds 1·5 l/day for more than 5–7 days in an adult or more than 100 ml/day in a child. Parietal pleurectomy is the most successful treatment when no distinct chylous leak can be identified. Less commonly, an isolated chylous leak either in the chest or in the abdomen may be identified and this should be treated by direct ligation.

Chylothorax is a rare condition characterized by the accumulation of a fluid containing chylomicrons within the pleural cavity. It may be caused by primary lymphatic disease but is more often secondary to intrathoracic malignancy, trauma or surgery. Most patients present with shortness of breath and a pleural effusion. The diagnosis is confirmed by biochemical and microscopic examination of the effusion and the cause defined by investigation of the state of the chest wall, pleura, lung substance, intrathoracic lymph nodes, pulmonary lymphatics and thoracic duct.

Patients and methods

All patients with a spontaneous chylothorax seen between 1956 and 1986 by the first author have been reviewed. They comprised nine men and 11 women with a median age at presentation of 33 years (range 9 months to 78 years). Fourteen patients presented with shortness of breath or a chest infection. Two patients presented with the very rare symptom of coughing up chyle mixed with sputum – chylous bronchorrhoea. The remainder presented with symptoms related to their primary disease, their effusions being detected by routine chest radiographs performed as part of the investigation of lymphoedema of the limbs or ascites. All but one underwent bipedal lymphangiography. As a result of these investigations the patients have been divided into two groups, primary chylothorax and secondary chylothorax.

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Primary chylothorax (Tables 1 *and* 2)

This group contained ten patients who had no cause for the chylothorax other than a primary abnormality of the lymph conducting system. Their median age at presentation was 16 years (range 9 months to 48 years).

Three patients (5, 8 and 10) had mediastinal megalymphatics and three (2, 3 and 7) had a chylous ascites which had refluxed across the diaphragm into the pleural cavities. One patient (9) had atresia of the thoracic duct (*Fig. 1*) and one (6) had a localized chylous leak from the hilum of the lung. In one child

Table 1 Presentation, management and outcome of patients with primary chylothorax

Patient no.	Age	Presentation	Diagnosis	Treatment	Outcome
1	9 months	Chest infection	Lymphatic deficiency?	None	Unknown
2	4 years	Abdominal swelling	Ascites/reflux	Laparotomy/pleurectomy	Died at 3 years
3	12 years	Incidental finding	Ascites/reflux	Laparotomy/LeVeen shunt	Unknown
4	9 months	Incidental finding	Lymphangiectasia	MCT oil	Well at 10 years
5	22 years	Dyspnoea	Megalymphatics	Pleurectomy	Well at 22 years
6	11 years	Dyspnoea	Hilar lymph leak	Pleurectomy	Well at 12 years
7	48 years	Dyspnoea	Ascites/reflux	Pleurectomy	Well at 3 years
8	34 years	Dyspnoea	Megalymphatics	Pleurectomy	Died at 2 years
9	16 years	Dyspnoea	Thoracic duct atresia	Pleurectomy/lymphovenous anastomosis	Well at 4 years
10	7 years	Dyspnoea	Megalymphatics	Pleurectomy/lymphovenous anastomosis	Well at 5 years

MCT, medium-chain triglyceride

(1) no diagnosis was made as the parents refused permission for a lymphangiogram. This child had oedema of the face and legs at birth and was believed, on clinical grounds, to have lymphatic aplasia but was lost to follow-up.

Table 2 Summary of patients with primary chylothorax

Patients	Treatment	Outcome
Ten patients (median follow-up 7 years)	Five pleurectomy Two lymphovenous anastomosis + pleurectomy One MCT oil One LeVeen shunt One no treatment	Six alive and well Two dead Two unknown

Four patients received dual modality treatment. MCT, medium-chain triglyceride

Seven of the ten patients were treated by surgical parietal pleurectomy and in two (9 and 10) a simultaneous lymphovenous anastomosis was made between the azygous vein and the thoracic duct; both of these anastomoses were shown to have occluded within a year of operation. One patient (4) was treated with a fat-free diet and medium-chain triglyceride (MCT) oil supplements alone, and one patient (2) whose chylothorax appeared to be secondary to chylous ascites had a laparotomy and ligation of the leaking peritoneal lymphatics. One patient (3) was treated with a LeVeen shunt (Becton Dickinson, New Jersey, USA) but was lost to follow-up. One further patient (1) in this group was lost to follow-up and two patients are known to have died, one (8) with fibrosed lungs 2 years after a pleurectomy for megalymphatics and one (2) 3 years after having bilateral pleurectomies. Five patients treated with pleurectomy were alive and free from effusion 3–22 years after surgery, and the one child treated with MCT oil alone had no effusion 10 years later. The outcome of the patients with primary chylothorax is summarized in *Table 2*.

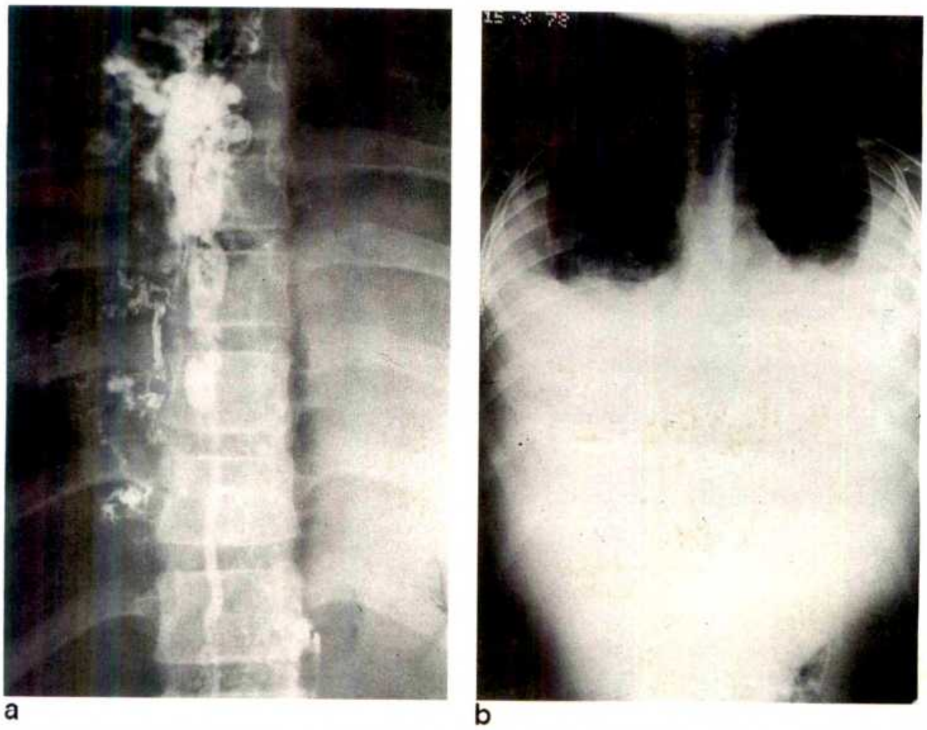

Fig. 1 **a** A normal sized lower thoracic duct enters a congenitally malformed ectatic middle and upper duct. Lipiodol can be seen to be entering the paravertebral and intercostal lymphatics confirming that this abnormality was obstructing normal cephalad lymph flow. **b** Lymphangiogram of a young teenage boy (patient 9) who presented with severe bilateral chylothorax

Table 3 Presentation, management and outcome of patients with secondary chylothorax

Patient no.	Age (years)	Presentation	Diagnosis	Treatment	Outcome
11	78	Dyspnoea	Lymphoma	MCT oil/aspiration	Died at 3 years
12	20	Dyspnoea	Filariasis	Lympho–venous anastomosis	Died at 3 months
13	70	Dyspnoea	Reticulum cell sarcoma	Radiotherapy	Unknown
14	66	Abdominal mass	Lymphoma	Radiotherapy	Died at 1 year
15	46	Swollen arms	Subclavian vein thrombosis	Pleurectomy	Died at 4 years
16	44	Dyspnoea	Lymphoma	Chemotherapy	Well at 6 years
17	52	Dyspnoea	Carcinoma of the cervix	Radiotherapy/pleurectomy	Well at 12 years
18	50	Dyspnoea	Lymphoma	Chemotherapy/pleurectomy	Well at 10 years
19	52	Dyspnoea	Lymphoma	Radiotherapy	Died at 1 year
20	30	Chest wall deformity	Idiopathic osteolysis	Pleurectomy	Well at 5 years

MCT, medium-chain triglyceride

Secondary chylothorax (Tables 3 *and* 4)

This group contained ten patients in whom the lymphatic obstruction was caused by another disease arising outside the lymph-conducting vessels. Their median age at presentation was 59 (range 20–78) years.

Seven of the ten patients had either a lymphoma or secondary malignant disease in the mediastinal lymph nodes, or lung lymphatics or tumour obstructing the thoracic duct (*Fig. 2*). One patient (15) had bilateral subclavian vein thromboses, one patient (12) had a chylothorax secondary to filarial fibrosis of the mediastinal and supraclavicular lymph nodes, and one patient (20) had a massive idiopathic osteolysis of the clavicle, first rib and sternum (*Fig. 3*).

Two (14 and 19) of the five patients with lymphomas had radiotherapy alone and both died within 1 year. Another patient (11) had repeated pleural aspirations combined with a low-fat diet and MCT dietary supplements and he also died 3 years after diagnosis. One patient (16) had chemotherapy alone and another (18) had chemotherapy and a surgical pleurectomy; both are alive and free of effusions 6 and 10 years respectively after treatment.

Surgical parietal pleurectomy was performed in three further patients; one (15) with bilateral subclavian vein thromboses, one (20) with sternal osteolysis and one (17) with metastatic carcinoma of the cervix who also had radiotherapy. Two of these patients (17 and 20) were alive and well 12 and 5 years after treatment respectively.

The patient (12) with a chylothorax secondary to a filarial infection had a thoracic duct–azygous vein anastomosis without a

Table 4 Summary of patients with secondary chylothorax

Patients	Treatment	Outcome
Ten patients (median follow-up 4 years)	Four pleurectomy One lymphovenous anastomosis Four radiotherapy Two chemotherapy One MCT oil	Four alive and well Five dead One unknown

Three patients received dual modality treatment. MCT, medium-chain triglyceride

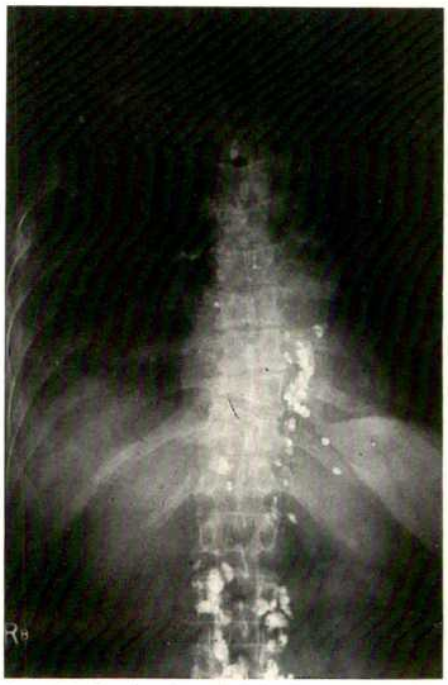

Fig. 2 Patient 17 who developed chylothorax secondary to an obstruction of the thoracic duct caused by secondary carcinoma of the cervix in the mediastinal lymph glands; 48 h after lymphangiography lipiodol was still trapped in the mediastinum below the level of the eighth thoracic vertebra. This patient is alive and well 12 years after a course of radiotherapy and pleurectomy

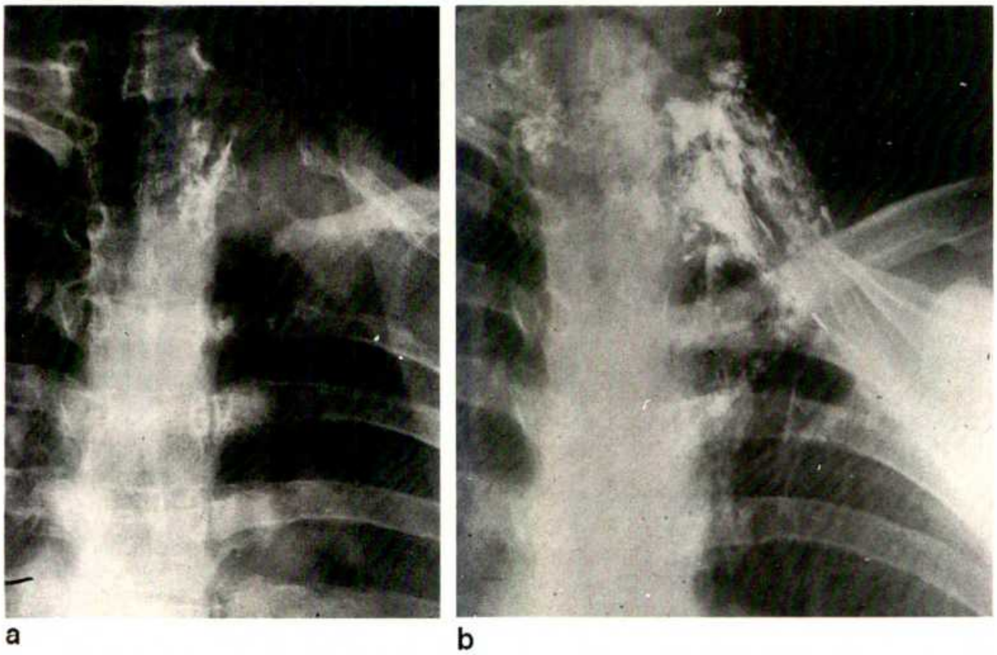

Fig. 3 **a** Idiopathic osteolysis (disappearing bone disease) in patient 20, affecting the upper three ribs associated with left-sided chylothorax. **b** A lymphangiogram of this patient shows a total obstruction of the terminal portions of the thoracic duct. Secondary and primary malignant disease in the supraclavicular area may have a similar effect

pleurectomy. The anastomosis occluded and the patient died from extensive pulmonary fibrosis 3 months after surgery. One patient (13) with a chylothorax secondary to a reticulum cell sarcoma had radiotherapy alone but has been lost to follow-up. The management and outcome of the patients with secondary chylothorax is summarized in *Table 4*.

Discussion

Although the condition is rare, the commonest cause of chylothorax is trauma, either following surgery of the great vessels[1] or the oesophagus[2,3], or following penetrating wounds or hyperextension of the spine[4,5]. Interestingly, no such aetiology could be identified in any of these patients with secondary chylothorax.

Spontaneous chylothorax, caused by primary lymphatic disease, malignancy or filariasis is much less common. Most cases of spontaneous chylothorax present with symptoms related to the pleural effusion. A chest radiograph is the initial investigation of choice and the presence of chyle in the pleural cavity is confirmed by lipid analysis of fluid from a pleural aspiration. The lipid content is usually in the range 4–40 g/l, typically with a high triglyceride and low cholesterol concentration[6], but the pathognomonic finding is the microscopic demonstration of chylomicrons.

Bipedal lymphangiography should be performed on all patients, both to demonstrate the anatomy of the thoracic duct and to indicate the cause of the chylothorax. Demonstration of the thoracic duct requires serial radiographs taken over a 2- or 3-h period; passage of lipiodol into the duct can be accelerated by elevation, massage or exercise of the legs[7]. These radiographs may show a primary abnormality of the thoracic duct, or retroperitoneal or mediastinal lymphatics, and may demonstrate the site of chyle leakage, in the chest or abdomen. A computed tomogram may be useful in demonstrating enlarged mediastinal or abdominal lymph nodes.

A few of the commoner causes of chylothorax are shown diagrammatically in *Fig. 4*. Congenital atresia of the upper part of the thoracic duct (*Fig. 4a*) or a congenital lymphangiectatic malformation (*Fig. 4b*) may both cause the development of a lymphatic–pleural fistula and chylothorax. If the lymphangiectasis involves the lung lymphatics the chyle may seep through the visceral pleura not only into the pleural space but also into the lung parenchyma, and the patient may cough up chyle. Such patients slowly develop a thick fibrous lung which may not expand to fill the thoracic cage after aspirating the effusion.

Secondary chylothorax is usually caused by disease in the mediastinal lymph nodes (*Fig. 4c*) or by traumatic or surgical interruption of the upper part of the thoracic duct. Occasionally the only source of the chyle in the chest is in the abdomen, the chylous ascites usually being caused by a congenital abnormality of the retroperitoneal lymphatics (*Fig. 4d*). In the absence of a patent pleuroperitoneal connection the chyle must reach the chest through aberrant lymphatics which have developed to bypass the abdominal lymphatic abnormality.

The general principles of treatment are as follows: (a) reduce the production of chyle; (b) treat the underlying cause; (c) intrapleural drainage with appropriate fluid replacement; and (d) obliteration of the pleural space.

A fat-free diet together with MCT supplements will reduce the quantity of chyle flowing through the thoracic duct, thereby reducing the leak into the pleural cavity and occasionally promoting spontaneous closure of a chylous fistula. This regimen alone was only successful in one (4) of the patients in this series but it also produced some amelioration of symptoms in others.

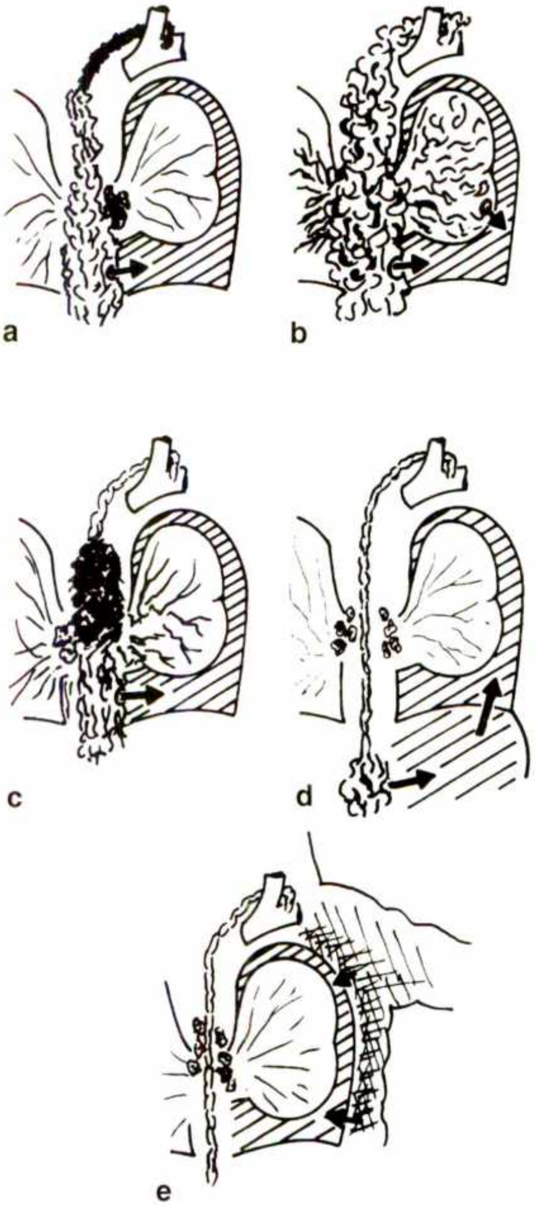

Fig. 4 Diagrammatic representation of the main causes of chylothorax. **a** An obstruction to the upper end of the thoracic duct, usually a congenital aplasia, but sometimes local malignant disease, causing downstream dilatation and a lymphatic–pleural fistula. **b** Congenital lymphangiomatous megalymphatic deformation of the whole of the thoracic duct causing a lymphaticopleural fistula, reflux of lymph into the substance of the lungs and effusion of lymph through the visceral pleura. **c** Mediastinal malignant disease in the mediastinal lymph nodes, causing obstruction and the development of a lymphatic–pleural fistula. **d** Chylous ascites leaking into the pleural space through a patent foramen in the diaphragm or collateral lymphatics. **e** Gross oedema of the upper limb and trunk may leak into the pleural cavity, but this lymph contains no fat and the effusion is *not* a chylothorax

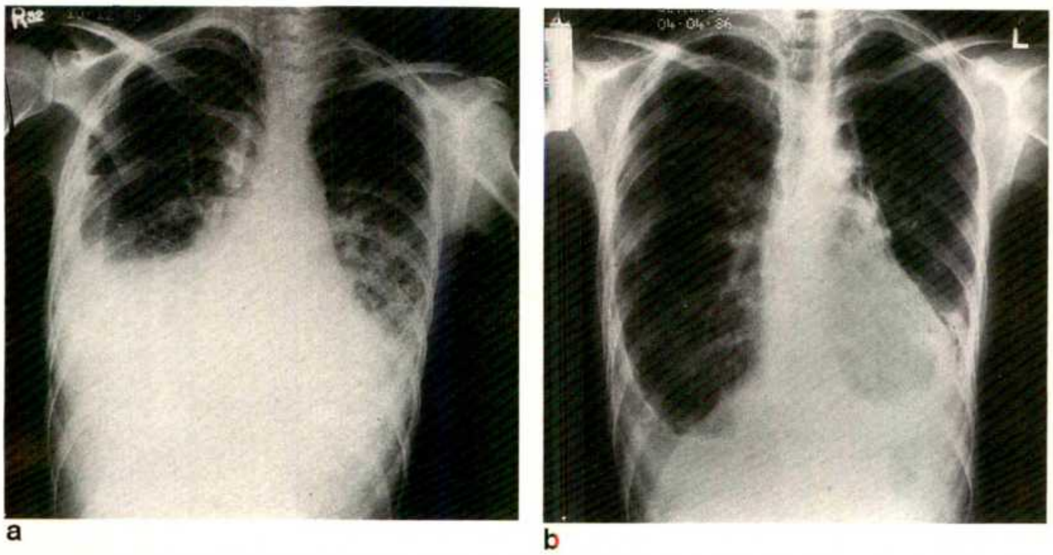

Fig. 5 **a** Very long-standing chylothorax in patient 8. The radiograph shows lipiodol refluxing into the substance of both lungs. The patient had a congenital thoracic duct atresia and presented with severe dyspnoea and chylous bronchorrhoea. **b** In spite of decortication at the time of pleurectomy followed by prolonged suction the thickened, fibrotic right lung of this patient would not expand to fill the whole pleural cavity

When the chylothorax is secondary to malignant disease, treatment of the primary condition with radiotherapy and/or chemotherapy may relieve the thoracic duct obstruction sufficiently to prevent reaccumulation of the effusion. Three patients (14, 16 and 19) with lymphoma and one with a reticulum cell sarcoma (13) were treated in this way. Although the chest symptoms were alleviated, the course of the disease was arrested in only one. Occasionally, a single or localized collection of chylous fistulas may be detected by lymphangiography and identified at thoracotomy after the injection of Patent Blue Violet into the web spaces of the feet[8], or by giving the patient a drink of creamy milk 2 h before operation[9]. A single fistula may be closed directly. A leaky patch of dilated lymphatics may sometimes be imbricated or oversewn, although in the latter case it is sometimes difficult to find healthy tissue without abnormal lymphatics to close the sponge-like leaking area.

Repeated drainage or continuous drainage of the effusion is rarely effective and can result in fluid losses of up to 2·5 l/day, with a reduction of plasma proteins and electrolytes. Such treatment should not be used for more than 5–7 days if the fluid loss exceeds 1·5 l/day in an adult, or more than 100 ml/day in a child[10]. All daily losses should be replaced intravenously.

The authors' early experience of pleurodesis with talc, silver nitrate, tetracycline, etc. was disappointing, because of the rapid rate of reaccumulation of the effusion. The reaccumulation of chyle can only be prevented by formal surgical pleurectomy and even this may not work if large quantities of chyle are entering the pleural space through the lung substance. When the problem is bilateral, sequential thoracotomies are performed 2–3 weeks apart. Pleurectomy is performed at thoracotomy through the bed of the sixth rib. The effusion is aspirated and the whole of the parietal pleura stripped from the inner surface of the

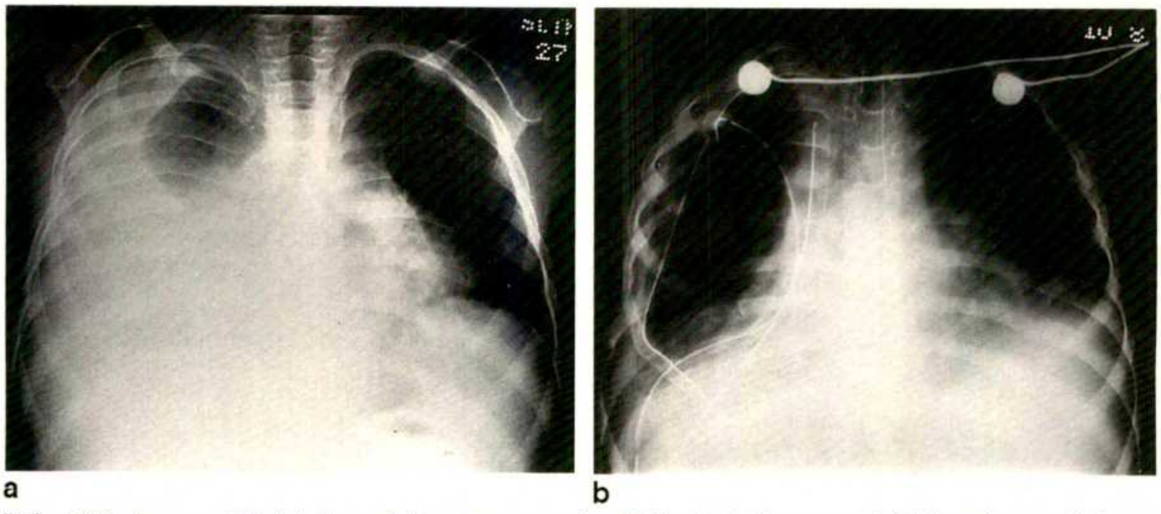

Fig. 6 **a** Patient 10 had severe right chylothorax. **b** In contrast to patient 8 (*Fig.* 5), the lung expanded fully and eventually became adherent to the chest wall after 3 weeks of intrapleural suction

ribs, together with as much pleura from the mediastinum as possible, taking care not to damage the veins, nerves and arteries of the mediastinum or open or damage any mediastinal lymphatics. It is not usually possible to strip all the pleura off the diaphragm. Any remaining pleura should be abraided with a rough plastic pad. It is uncommon to find a thick layer of fibrin over the surface of the lung except in patients with very long-standing effusion. After the parietal pleurectomy, the lungs should be inflated to check that they will fill the thoracic cavity. If not, a decortication should be performed but is not always successful if the lungs themselves have become fibrotic (*Fig. 5*). Decortication also adds to the hazard of the whole procedure, as the inevitable air leaks from the lung surface impede the adhesion between the lung and the chest wall. Chest drains are inserted and left on low-pressure suction until the chyle leak stops. This sometimes takes 2–3 weeks (*Fig. 6*).

Occasionally chylothorax is secondary to chylous ascites, with reflux of chyle across the diaphragm into the pleural cavities. Stopping the abdominal lymphatic leak (by direct ligation of the fistula or excision of leaking bowel[10] or, if no leak can be identified, by use of a LeVeen shunt[11]) may prevent reaccumulation of the pleural effusions, unless there is a coexisting thoracic lymphatic abnormality.

Thoracic duct to azygous vein anastomosis has been attempted to relieve chylothorax secondary to thoracic duct obstruction[12], but in the authors' experience these anastomoses occlude at an early stage, presumably because the low lymphatic pressure present after the duct has been decompressed[13] allows the reflux of blood into the thoracic duct and subsequent thrombosis.

In summary, all patients with proven chylothorax should undergo lymphangiography to identify its causal mechanism and define the site of lymphatic abnormality. Conservative treatment with drainage of the effusion, a low-fat diet and use of MCT oil supplements is adequate in some patients. However, if the fluid loss exceeds 1·5 l/day for more than 5–7 days in an adult or more than 100 ml/day in a child, drainage should not be continued for more than a week, unless the concurrent treatment of an underlying malignancy is likely to produce resolution of a thoracic duct obstruction. Careful intravenous replacement of all fluid, protein and electrolyte losses is essential. When an isolated chylous leak is found either in the chest or in the abdomen, direct closure of the leak is likely to be successful. However, this situation occurs infrequently and, where no such leak can be identified, surgical parietal pleurectomy is the most successful treatment.

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Lazaroid improves intestinal blood flow in the rat during hyperdynamic bacteraemia

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Background Intestinal mucosal hypoperfusion and loss of barrier function during sepsis may contribute to maintaining the septic state. Free radicals are produced during sepsis and antioxidants improve survival from experimental sepsis. It is unclear whether endothelial cell injury from free radicals results in altered microvascular reactivity. Lazaroids are antioxidants which scavenge radicals and block lipid radical chain reactions. The authors sought to determine whether lazaroids altered the intestinal microvascular responses to sepsis.

Methods *In vivo* video microscopy was used to study the ileal microcirculation of the rat. A1 (inflow) arteriolar diameter and flow, A3 (premucosal) arteriolar diameters, and cardiac output were measured. Lazaroid or vehicle was infused before a bolus injection of live *Escherichia coli* or saline.

Results Lazaroid alone had no effect on the intestinal vessels or haemodynamics. *E. coli* caused vasoconstriction (A1, −21 per cent, A3, −19 per cent of baseline) and hypoperfusion (−36 per cent) despite increased cardiac output (+31 per cent). Lazaroid significantly attenuated both constriction (A1, −11 per cent; A3, 10 to −1 per cent) and hypoperfusion (−15 per cent), but did not increase cardiac output (30 per cent).

Conclusion *E coli* bacteraemia led to intestinal vasoconstriction and hypoperfusion. Lazaroid reduced this effect without altering central haemodynamic responses, suggesting that free radicals have a deleterious effect on the intestinal microcirculation during bacteraemia.

Multiple organ failure (MOF) still has a mortality rate of 40–50 per cent[1] Sepsis is a major factor in the development of MOF, which may persist despite control of the original infection[2,3]. Early sepsis leads to an increased cardiac output and normal blood pressure[4]. Despite the early hyperdynamic systemic circulation, the visceral microcirculation is underperfused[5]. The microvascular hypoperfusion of the splanchnic bed is believed to result in loss of mucosal barrier function which can lead to translocation of bacteria and their toxins. This is postulated to contribute to the perpetuation of the septic state and development of MOF[6]. The microvascular response of the intestinal microcirculation to sepsis is the result of a balance of vasoconstrictor and vasodilator influences. Vasoconstrictors, including platelet activating factor (PAF) and prostaglandins[7,8], are increased during sepsis. Other vasoactive factors such as nitric oxide and dilator prostanoids may be involved as compensatory mediators[9,10].

The production of free radicals and other reactive oxygen species (ROS) is a normal event for oxygen-utilizing biological systems. Under normal circumstances these radicals are quenched by endogenous scavenging systems. During sepsis there is excessive production of free radicals which leads to depletion of endogenous antioxidants and loss of protection against potential radical damage[11]. Free radicals have direct toxic effects on the structure and function of organic proteins and lipid membranes[12].

Antioxidants are able to reduce this process and have been shown to improve survival in animal models of sepsis[13]. Recent evidence suggests that ROS may be involved in modification of arachidonic acid metabolism and the direct production of lipid-derived vasoactive agents[14]. The role of ROS as mediators or modulators of the intestinal microcirculatory response to sepsis is unclear. Lazaroids such as U74389G are radical-quenching antioxidants, and have been shown to directly scavenge the primary free radicals superoxide and hydroxyl, inhibit the production of superoxide by neutrophils[15], scavenge secondary peroxyl radicals[16] and prevent the release of arachidonic acid metabolites from damaged cell membranes[17]. The authors hypothesized that lazaroid treatment may attenuate the intestinal microvascular response to bacteraemia.

Materials and methods

Animal preparation and haemodynamic measurements

Male Wistar rats, weighing 300–320 g, were acclimatized for 10 days at an animal care facility with free access to water and Purina rat chow (Purina, Richmond, Indiana, USA) Animal care and experiments were carried out with the approval of the University of Louisville and Veterans Administration Animal Care and Use Committee Food, but not water, was withheld at least 12 h before experimentation. Animals were anaesthetized with a single intraperitoneal injection of 5-ethyl-5-(1-methylpropyl)-2-thiobarbiturate sodium 100 mg/kg. Each animal received 5 ml/kg of normal saline subcutaneously after induction of anaesthesia to maintain adequate hydration during the experiment Temperature was maintained at 37 ± 0.5 °C with an autoregulated heating pad and a rectal probe. Tracheostomy was performed and animals breathed room air. For determination of cardiac output by transpulmonary thermodilution, a thermistor was placed in the proximal aortic root via the right carotid artery, and a cannula of PE50 tubing advanced to the right atrium via the right jugular vein. Cardiac output was calculated from time–temperature curves as previously described[18]. The left femoral artery was cannulated with PE90 tubing and mean arterial pressure (MAP) and heart rate monitored by a transducer (Micro-Med, Louisville, Kentucky, USA). The femoral vein was cannulated with PE50 tubing to allow administration of bacteria and drugs

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A right paramedian abdominal incision was made and a 3-cm section of terminal ileum with intact neurovascular supply was exteriorized. The intestinal segment was divided along its antimesenteric side with cautery and suspended over the optical port of a tissue bath. During preparation and subsequent observation the intestine was bathed with a modified Krebs' solution (sodium carbonate 25·5 mmol/l, sodium chloride 112·9 mmol/l, potassium chloride 4·7 mmol/l, calcium chloride 2·55 mol/l) which was bubbled with carbon dioxide and nitrogen to maintain a pH of 7·4 ± 0·05 and warmed to 37 ± 0·5°C. The preparation was positioned on a stage of a compound trinocular microscope for direct and closed circuit television microscopy. Isoproterenol hydrochloride was added to the bath (1×10^{-8} g/ml) to decrease peristalsis. This concentration is 1000 times less than that reported to affect small intestinal microvascular diameter or reactivity[19].

Measurements of vessels

After allowing 45–60 min for haemodynamic and tissue conditions to equilibrate, baseline measurements of haemodynamic parameters (MAP, heart rate and cardiac output) and microvascular diameters and flow were made. Microvascular anatomy was defined according to branch order described by Gore and Bohlen[20]. First-order arterioles (A1), or inflow vessels, originate from the mesenteric arcade and penetrate the outer muscular layers of the bowel into the submucosa. Second-order arterioles (A2) branch from A1 and run longitudinally in the submucosa. Third-order arterioles (A3) are right angle branches of A2 and penetrate the mucosa as central villus arterioles (premucosal). Images were recorded on video tape throughout the experiment. Intraluminal diameters were measured off-line using a calibrated electronic video calliper (Microcirculation Research Institute, Texas A and M University, College Station, Texas, USA). Centre line intravital red cell velocity in the A1 was measured using an optical Doppler velocimeter (Microcirculation Research Institute). Blood flow was calculated as previously described[5].

Preparation of bacteria

Escherichia coli were cultured from a hospital acquired pathogenic strain kept frozen in fresh medium. Before each experiment, bacteria were thawed and incubated in tryptose–soy agar at 37°C for 18 h to produce a stationary growth phase culture. Bacteria were then centrifuged, washed twice with normal saline and resuspended in normal saline. Serial dilutions were measured spectrophotometrically at 500 μm wavelength to provide 1×10^8 bacteria per ml. A dose of 4×10^8 bacteria per 100 g was administered through the femoral vein catheter over 5 min.

Lazaroid U74389G

U74389G was dissolved in a citrate vehicle (Upjohn, Kalamazoo, Michigan, USA) at a concentration of 2 mg/ml. A dose of 6 mg/kg was used (made up to 1ml with normal saline). This dose was administered 30 min before the start of bacteraemia.

Experimental protocol

A total of 19 animals in three groups were studied. Group 1 (*n* = 6) served as control; lazaroid U74389G 6 mg/kg was infused over 5 min, and measurements made every 15 min for the course of the experiment. Thirty minutes after lazaroid 1ml saline was infused over 5 min. Group 2 (*n* = 6) was used to characterize the effects of *E. coli* on the intestinal microcirculation during basal conditions. Baseline measurements were made and a control infusion of lazaroid vehicle given. After 30 min 4×10^8 bacteria per 100 g in 1 ml saline was infused over 5 min. Observations were recorded every 15 min for 2 h. Group 3 (*n* = 7) was used to study the effects of lazaroid treatment on the vascular sequelae of *E. coli* infusion. After baseline measurements, lazaroid infusion was initiated as described above, and 30 min later *E. coli* were infused as outlined.

Statistical analysis

All data are expressed as percentage change from baseline. All measurements were made in triplicate over a 30-s period and the mean of these values is reported. The mean(s.e.m.) was calculated for each group at each time point and compared with baseline values (non-normalized) using repeated analysis of variance and Dunnett's test. Comparisons among groups were performed by analysis of variance and Tukey's honestly significant difference test. Differences were considered significant at $P < 0·05$

Results

There was no significant difference among baseline values for the three groups (*Table 1*).

Systemic haemodynamic variables (Fig. 1)

Infusion of U74389G had no effect on systemic haemodynamic variables. Infusion of *E. coli* produced a hyperdynamic response: mean(s.e.m.) cardiac output increased significantly to a maximum at 90 min (+31·4 (5·9) per cent of baseline); thereafter cardiac output began to decrease but remained raised at 2 h (+16·1(5·4) per cent). MAP was not significantly altered. Heart rate increased over 2 h, peaking at +14·9(3·8) per cent at 90 min. Lazaroid treatment before *E. coli* bacteraemia did not alter the central response to sepsis.

Intestinal microvascular variables (Figs. 2 *and* 3)

Vessel diameters and flow were unaffected by U74389G infusions. *E. coli* infusion (group 2) produced rapid and progressive vasoconstriction. A1 diameter decreased over 120 min to −20·6(2·5) per cent of baseline. A1 flow was temporally related to A1 vasoconstriction, with a nadir at the same time point (−36·4(2·3) per cent). A3 (premucosal) arterioles constricted to 18·7(2·5) per cent below baseline at 120 min. Lazaroid treatment before bacteraemia significantly attenuated the A1 vasoconstriction and hypoperfusion seen in group 2. A1 diameter fell to only −11·3(1·4) per cent at 120 min. A1 flow fell to only −14·9(7·5) per cent at 120 min. Interestingly, lazaroid treatment resulted in preservation of A3 arteriolar diameters during subsequent bacteraemia (group 3), peaking early at 9·6(5·5) per cent at 15 min and falling only to baseline at 120 min (−0·9(5·5) per cent).

Table 1 Summary of baseline values for all groups

	Lazaroid (*n* = 6)	*E. coli* with vehicle (*n* = 6)	*E. coli* with lazaroid (*n* = 7)
Heart rate (beats per min)	337(19)	341(5)	341(12)
MAP (mmHg)	90(4)	104(3)	111(6)
Cardiac output (ml per min per 100 g)	20·9(3·1)	23·1(1·5)	24·3(2·2)
A1 diameter (μm)	103·8(9·8)	105·6(9·3)	103·3(7·0)
A1 flow (nl/s)	10·9(1·9)	9·3(1·0)	9·6(1·8)
A3 diameter (μm)	14·1(1·7)	16·3(1·4)	16·5(0·8)

Values are mean(s.e.m.). MAP, mean arterial pressure

Discussion

In this study, *E. coli* infusion produced mesenteric vasoconstriction and hypoperfusion, despite a hyperdynamic systemic circulation. The major finding was that U74389G attenuated the microvascular response to bacteraemia, reducing A1 vasoconstriction and hypoperfusion and completely preventing A3 (or premucosal) vasoconstriction, despite little to no effect on the systemic haemodynamic response.

The gut is particularly sensitive to the effects of vasoactive agents[21] and hypoperfusion[22]. During sepsis, decreased mesenteric blood flow leads to loss of mucosal function[23]. The severity and duration of intestinal hypoperfusion is strongly associated with the subsequent development of MOF[24].

Bacteraemia leads to exaggerated ROS production, most likely through two mechanisms: activated neutrophils (prevalent in intestinal submucosa) undergo a respiratory burst and superoxide production[25], and increased arachidonic acid metabolism leads to enhanced ROS production[26]. Investigations of the mesenteric vascular responses to sepsis indicate that arachidonic acid derivatives play a major role in regulating splanchnic microcirculatory flow. Thromboxane A_2, leukotrienes and PAF lead to mesenteric vasoconstriction and act as chemoattractants[10,27,28]. Vasodilators such as prostacyclin (PGI_2) and nitric oxide act to attenuate or reverse vasoconstriction[9,29–31]. Free radical production is linked to, and can modulate the production of, these vasoactive derivatives. The enzymatic reduction of hydroxy fatty acids during leukotriene synthesis leads to hydroxyl radical production[26], and inhibition of prostacyclin synthase and cyclo-oxygenase. This may be a form of negative feedback under normal circumstances, but with increased leukotriene turnover may be detrimental, through loss of PGI_2 production. Additionally it has been shown that through a non-enzyme dependent mechanism, ROS-induced lipid peroxidation produces prostanoids termed F2-isoprostanes, which have powerful vasoconstrictive effects[14] and have been implicated in a number of ROS-induced pathologies[32]. Free radicals have direct effects on vasoactive processes. Hydrogen peroxide is thought to activate membrane-bound phospholipase

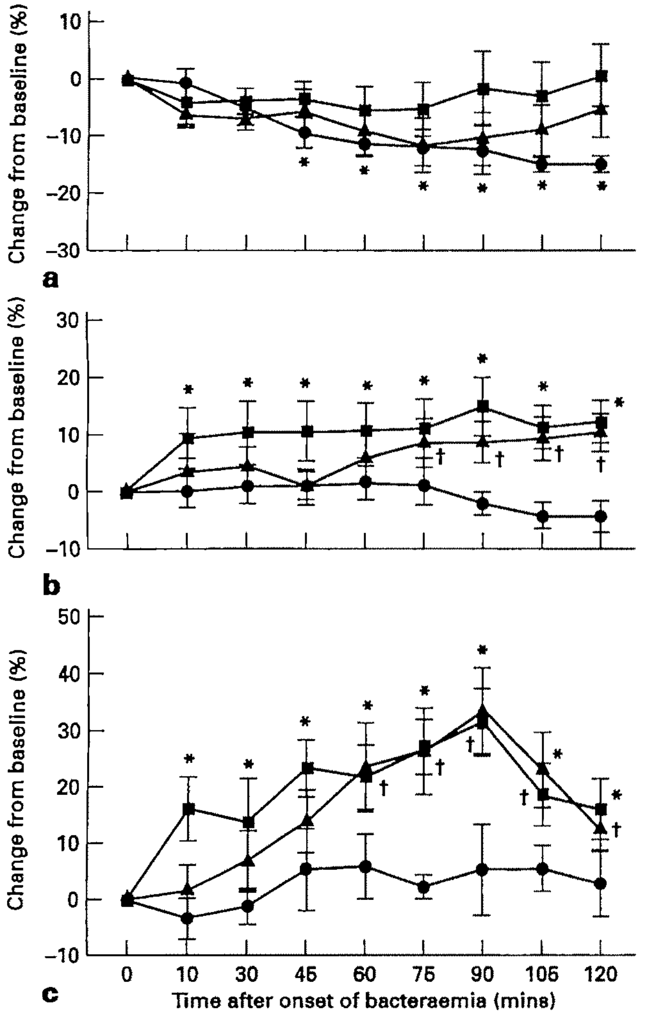

Fig. 1 Central haemodynamic changes for all three groups Values are percentage change from baseline(s.e.m.). a Mean arterial pressure; b heart rate; and c cardiac output ●, Lazaroid; ■, *E coli*; ▲, *E coli* and lazaroid $^*P<0{\cdot}05$, *E coli versus* lazaroid; $†P<0{\cdot}05$, *E. coli* and lazaroid *versus* lazaroid

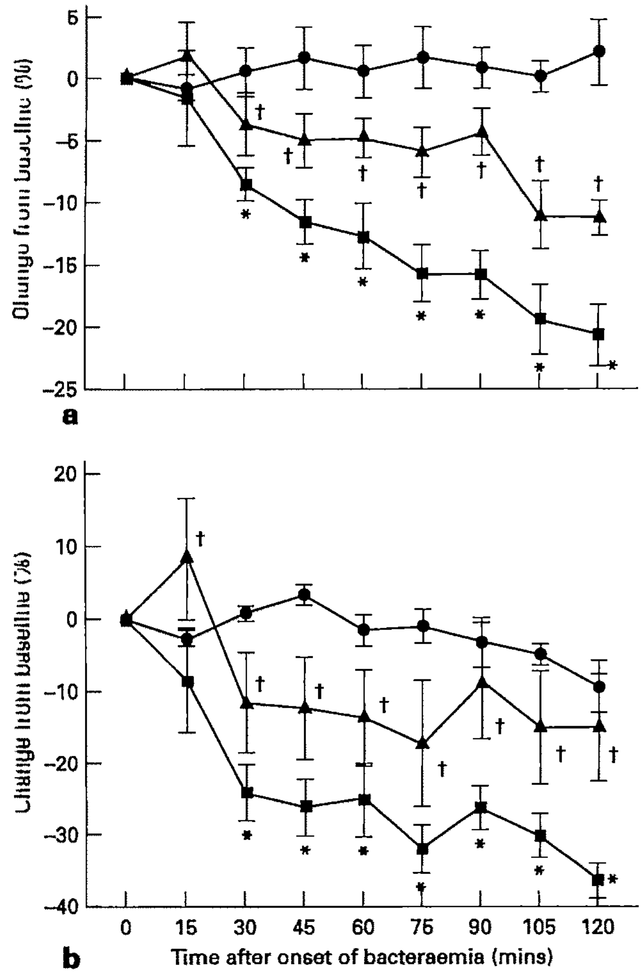

Fig. 2 A1 diameter (a) and A1 flow (b) changes for all three groups. Values are percentage change from baseline(s.e.m.) ●, Lazaroid; ■, *E. coli*; ▲, *E. coli* + lazaroid. $^*P<0{\cdot}05$, *E. coli versus* lazaroid, $†P<0{\cdot}05$, *E. coli* and lazaroid *versus E. coli*

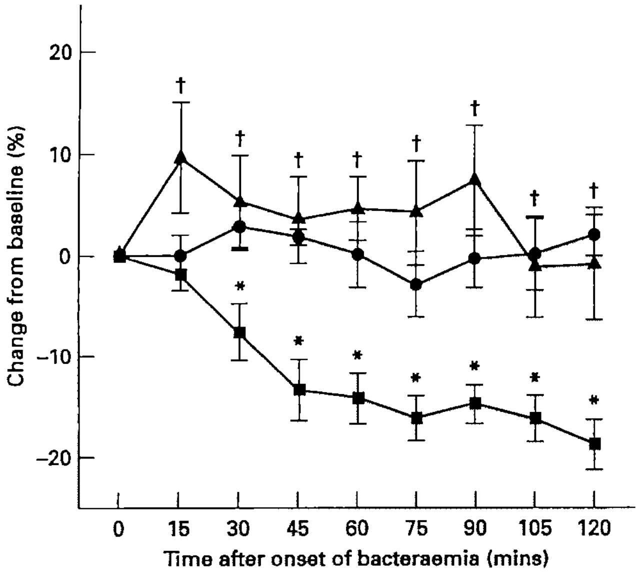

Fig. 3 A3 diameter changes for all three groups. Values are percentage change from baseline(s.e.m.). ●, Lazaroid; ■, *E coli*; ▲, *E. coli* and lazaroid. **P* < 0·05, *E coli versus* lazaroid; †*P* < 0·05, *E coli* and lazaroid *versus E coli*

A_2[33] providing substrate for prostanoid and PAF production. Nitric oxide, itself a free radical, is produced during sepsis; it may react with superoxide to form peroxynitrite, decomposing to the highly toxic hydroxyl radical[34].

Antioxidants have been shown to inhibit lipid peroxidation and improve survival in models of sepsis[13,35,36]. U74389G is a 21-aminosteroid or lazaroid. It has been shown to directly scavenge peroxyl radicals. Lazaroids compete with and conserve vitamin E (α-tocopherol), a powerful, and structurally similar, endogenous antioxidant[16]. Tirilazad (a structurally almost identical lazaroid) is a potent scavenger of the hydroxyl radical, a weak scavenger of the superoxide radical, and inhibitor of nicotinamide adenine dinucleotide phosphate oxidase in neutrophils (responsible for superoxide generation)[15]. Lazaroids are able to inhibit ROS generation by human leucocytes[37]. Lazaroids also have a stabilizing effect on lipid membranes and are able to block the release of arachidonic acid and vasoactive isoprostanes from injured cell membranes[17,38]. This is not a glucocorticoid effect (i.e. phospholipase A_2 inhibition), but may be an antioxidant effect. Tirilazad has been shown to localize within the hydrophobic core of the phospholipid bilayer of endothelial cells[39] and thus may inhibit ROS-induced propagation of lipid peroxidation by restricting the movement of lipid peroxyl radicals within the membrane. Lazaroids improve mesenteric blood flow after periods of ischaemia, but have additional protective effects on the mucosa which are not entirely due to improved total blood flow[40]. In the intestine, lazaroids preserve the production of PGI_2 after burn injury[41]. The role of nitric oxide in preserving vessel diameters during sepsis has been demonstrated by the authors' previous findings[9]. By inhibiting superoxide production and scavenging hydroxyl radicals lazaroids may preserve the vasodilator capacity of nitric oxide production.

The beneficial effects of lazaroid on the intestinal microcirculation during sepsis are probably the result of a combination of several of these properties. The authors' previous studies have demonstrated that sepsis leads to microvascular vasoconstriction and loss of mucosal blood flow. Lazaroids attenuate mucosal hypoperfusion, possibly by inhibiting oxidant driven production of vasoactive isoprostanes and PAF, and by preserving the production of vasodilators and cytoprotective agents such as nitric oxide and PGI_2. Whether these effects are due to local actions on endothelial cell membranes or on circulating factors remains to be determined.

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Short note

Parental attitude in children referred for circumcision

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Circumcision is usually performed for medical reasons, most commonly phimosis[1–3]. The foreskin develops normally in 95 per cent of boys by 5 years of age[4] and in 99 per cent by 15 years[5]; however, up to 6 per cent of boys in Mersey region were circumcised by the age of 15 years[1]. This highlights a discrepancy in the expected and observed circumcision rate. One possible reason could be that parental pressure may be brought to bear, in favour of circumcision. General practitioner referrals were audited to assess the effect of parental attitude on the clinical decision for circumcision.

Patients and methods

All referrals for circumcision were studied prospectively for 6 months Patient symptoms, reasons for referral, the parents' view and referral diagnosis were documented. The grade of assessing surgeon, physical findings and outcome, parental attitude to circumcision and whether parental pressure influenced the final clinical decision were recorded. To ensure clinical uniformity, patients seen by junior staff in the first 2 months of the study were also seen by the consultant. Phimosis was defined by the presence of scarring, fissuring or fibrosis of the foreskin and was a clinical diagnosis.

Results

Seventy-seven boys (median age 5 years 5 months, range 5 months to 13 years 11 months) were seen. Presenting symptoms were: balanitis (27 patients), tight foreskin (25) and ballooning on micturition (15). General practitioners' referral diagnoses were: tight foreskin (31), phimosis (23) and balanitis (21). One child was referred with a long redundant foreskin and one had penile bleeding. Examination findings are presented in *Table 1*.

Fifty-six boys (73 per cent) had a healthy foreskin which was either retractile (22 patients) or non-retractile (34), and 21 boys had phimosis. Twenty-six boys (34 per cent) were listed for circumcision for phimosis (21 patients) and re-referral for persistent problems (two, both by consultants). Three children with non-retractile foreskins and balanitis were listed because of age (12 and 9 years) and parental influence (one child). The median age of these 26 boys was 5 years 5 months (range 2 years 7 months to 14 years 6 months). There was no significant difference in the decision for circumcision between consultants (29 per cent) and senior house officers (45 per cent; $\chi^2 = 1{\cdot}73$, 1 d.f., P not significant) or higher surgical trainees (22 per cent, $\chi^2 = 0{\cdot}23$, 1 d.f., P not significant).

Table 1 Correlation between referral diagnosis and examination findings

	Referral diagnosis				
Examination findings	Tight foreskin	Phimosis	Balanitis	Other	Total
Healthy retractile foreskin	10	4	7	1*	22
Healthy non-retractile foreskin	19	7	8	0	34
Phimosis	2	12	6	1†	21

*Child with a long redundant foreskin; †child with penile bleeding

The majority (56; 73 per cent) of parents had attended for further advice or reassurance with only 13 specifically requesting circumcision. Fifty-nine parents (77 per cent) were neutral or against circumcision. Eighteen (23 per cent) were in favour of circumcision. For boys with a healthy retractile (22) and non-retractile (34) foreskin, parental attitude was neutral in 36 cases, against in ten and for circumcision in ten cases. Of those 26 boys listed for circumcision, parental attitude was negative or neutral in 16 and favoured circumcision in ten cases ($\chi^2 = 2{\cdot}36$, 1 d.f., P not significant). In 22 of these children parental pressure made no contribution to the decision for circumcision. Two parents declined advice for circumcision. For one child the decision was positively affected as he was re-referred twice and for only one boy did the parents' views markedly influence the surgeon's decision in a positive way for circumcision.

Discussion

For most boys, preputial separation occurs by 5 years of age[4]. Reassuringly, in this series the median age of children for circumcision was 5 years 5 months. The final circumcision rate of 34 per cent is somewhat higher than that of 28 per cent reported in Liverpool[1] and 20 per cent from Nottingham[2]. Reasons for this are speculative, but may reflect a more informed referral practice by local general practitioners or a lower threshold for circumcision by the Leicester consultants. The grade of assessing clinician was not significant. In this study, most parents were neutral towards circumcision and were happy to accept medical advice. Likewise, for the majority of children (22 of 26) requiring circumcision, parental pressure played no or very little part in influencing the final decision. Whatever the complex reasons for the discrepancy in the expected and observed circumcision rate, this study suggests that parental pressure is unlikely to be a significant factor.

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Short note

Internal sphincter spasm in anal fissure

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An anal fissure is a split in the skin of the distal anal canal characterized by pain on defaecation and rectal bleeding. It is associated with hypertonia of the internal anal sphincter (IAS). Traditionally it is thought that hypertonia is secondary to pain. However, it has been reported that pressure in the anal canal does not fall after abolition of pain from the fissure by application of local anaesthetic to the area, suggesting that the spasm may not be secondary to pain[1].

Standard surgical treatment for chronic anal fissure is internal anal sphincterotomy or anal dilatation. These procedures permanently lower resting anal pressure and lead to healing of the fissure in the majority of patients. However, both of these procedures may cause impairment of continence in up to 30 per cent of cases[2]. Recently, reversible 'chemical sphincterotomy' using topical 0·2 per cent glyceryl trinitrate (GTN) ointment has been described and healing in over two-thirds of patients has been reported[3]. This treatment has the potential advantage that there is no permanent damage to the IAS. The aim of this study was to assess the long-term effect of chemical sphincterotomy on maximum anal resting pressure (MARP).

Patients and methods

Twenty-three patients (nine women, median (range) age 38 (16–79) years) presenting with chronic anal fissure were treated with 0·2 per cent GTN ointment (Percutol; Dominion Pharma, Haselmere, UK) diluted 1:10 with white soft paraffin. MARP was measured before and 20 min after application of GTN on the first visit using a constantly perfused side-hole catheter using a method previously described[3]. All fissures healed after 4–8 weeks of treatment with GTN. A minimum of 3 months after the end of treatment patients were reviewed and manometry was repeated. Patients were asked if they had experienced any recurrent symptoms of bleeding or pain on defaecation.

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Results

Mean(s.d.) MARP fell from 116·3(44·6) cmH_2O before treatment with GTN to 66·3(29·7) cmH_2O 20 min after application of the ointment ($P < 0.001$, Student's paired *t*-test). Ten patients reported transient headache (<30 min) during treatment which was relieved with oral analgesia. Median (range) follow-up was 5 (3–11) months. At review mean(s.d.) MARP levels had returned to pre-treatment values (112·3(44·0) cmH_2O, $P = 0.34$, Student's paired *t* test) (*Fig. 1*). Eight subjects had experienced pain and rectal bleeding since cessation of treatment with GTN ointment. Six patients reported that their symptoms lasted only a few days. One patient's symptoms resolved spontaneously and a further three patients' symptoms resolved with dietary modification. Two patients treated recurrent symptoms themselves with remaining GTN ointment. Two patients re-presented 4 and 5 months after initial healing with recurrent anal fissures. Both patients were successfully treated with a further 6 weeks of 0·2 per

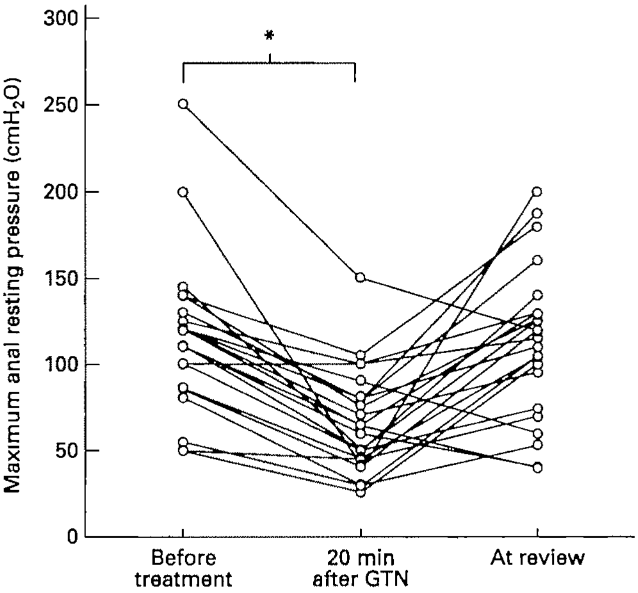

Fig. 1 Maximum anal resting pressure for individual patients before, 20 min after application of 0·2 per cent glyceryl trinitrate (GTN) ointment and at review (minimum 3 months after fissure healing). *$P < 0.001$ (Student's paired *t* test)

cent GTN ointment. There were no fissures present at review.

Discussion

This study demonstrates that MARP returns to pre-treatment levels after healing of chronic anal fissure following chemical sphincterotomy. Traditionally it has been thought that anal fissure is caused by tearing of the skin of the distal anal canal on passage of a hard stool bolus. However, only 25 per cent of patients report such an episode at the onset of their symptoms. It has been suggested that anal fissure may be an ischaemic ulcer[4], and a paucity of branches of the inferior rectal artery to the posterior midline of the distal anal canal has been demonstrated[5]. This poor supply is further compromised by hypertonicity of the IAS. Thus return to pre-treatment MARP in the anal canal following chemical sphincterotomy may render this area relatively ischaemic once more. Recurrent symptoms reported by patients treated by chemical sphincterotomy suggests that IAS hypertonicity may be causative in the pathogenesis of anal fissure. Although patients treated by chemical sphincterotomy may be at risk of recurrent anal fissure, these recurrences seem to be treated successfully with further GTN ointment.

Acknowledgements

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Synchronous upper and lower gastrointestinal endoscopy is an effective method of investigating iron-deficiency anaemia

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Background The investigation of iron-deficiency anaemia is often inadequate. Synchronous upper and lower gastrointestinal endoscopy under the same sedative episode (bidirectional endoscopy; BDE) has been proposed for all such patients.

Methods The value of this strategy has been examined prospectively. Eighty-nine patients with iron-deficiency anaemia underwent BDE using local anaesthesia of the throat and intravenous midazolam.

Results A cause for gastrointestinal blood loss was found in 75 patients (84 per cent) after BDE alone. Twenty-five patients (28 per cent) had upper gastrointestinal pathology alone, 24 (27 per cent) had lower gastrointestinal pathology alone and 26 (29 per cent) had dual pathology. Forty-five patients (51 per cent) had gastrointestinal malignancy. Twenty patients (22 per cent) had further investigations and these yielded a diagnosis in five. No cause for the anaemia was found in nine patients (10 per cent). Treatment of the bleeding source(s) resolved the anaemia in all but one patient.

Conclusion BDE is an effective investigation for patients with iron-deficiency anaemia and its use should be encouraged.

Iron deficiency is the commonest cause of microcytic hypochromic anaemia[1]. In men of all ages and post-menopausal women gastrointestinal blood loss is usually the cause. Investigation of these patients is often inadequate or delayed[2]. A recent audit found that 50 per cent of patients with iron-deficiency anaemia had either faecal occult blood testing alone or no investigation at all[3]. When further investigations were arranged only 19 per cent of patients had both the upper and lower gastrointestinal tract examined.

Endoscopy is a sensitive test for identifying bleeding sources in the accessible parts of the gastrointestinal tract. Whether the upper or lower gastrointestinal tract is examined first may be strongly influenced by the patient's symptoms but the correlation between symptoms and pathology is poor[4]. Having discovered pathology in the upper or lower part of the gastrointestinal tract there is a natural tendency to assume that this is the cause of the blood loss and not to investigate any further. Dual pathology, however, can be expected in about 16 per cent of an elderly population[1].

Previous studies of synchronous upper and lower gastrointestinal endoscopy (bidirectional endoscopy; BDE) have shown its value in the investigation of iron-deficiency anaemia[5,6] but this has not been widely adopted into practice. For the past 5 years all patients referred for investigation of iron-deficiency anaemia with non-specific symptoms have undergone BDE. The value of this approach has been analysed by reviewing all diagnoses and outcomes in such patients.

Patients and methods

During the 5 years from January 1991 to January 1996 BDE was performed in all patients with iron-deficiency anaemia without specific symptoms or signs who were referred for investigation to a consultant surgeon. Tiredness, lack of appetite and vague abdominal discomfort were common symptoms but patients with more specific symptoms such as change of bowel habit were excluded. Patients had BDE if their symptoms did not provide a clear indication of which part of the gastrointestinal tract was bleeding Iron-deficient anaemia was defined as a haemoglobin level below 13 g per 100 ml for men and below 11 5 g per 100 ml for women, with a low mean cell volume (less than 76 femtolitres) and low serum ferritin (less than 15 μg/l) Faecal occult blood testing was not done. The procedure was carried out as a day case and information on diagnoses collected prospectively Bowel preparation was with Kleenprep (Norgine, Harfield, UK).

Upper gastrointestinal endoscopy was performed after application of anaesthetic throat spray and intravenous midazolam sedation and followed by colonoscopy. All procedures were carried out by a consultant or senior registrar or a registrar under senior instruction. Oxygen was given by nasal cannula and oxygen saturation was measured by pulse oximetry. A 'J' manoeuvre was always performed as part of the upper gastrointestinal endoscopy and colonoscopy was considered complete if the ileocaecal valve was seen. If the caecal pole was not reached a barium enema was performed on the same day. All patients with a macroscopically normal upper gastrointestinal tract had duodenal biopsies taken to exclude coeliac disease. Mild mucosal inflammation was not considered a likely cause of blood loss and anaemia. Savary-Miller grade II[7] or worse oesophagitis, erosive gastritis or duodenitis with flecks of blood in the gut lumen and ulceration were considered to be likely causes of anaemia but mild inflammation, simple diverticular disease and small colonic polyps were not Patients requiring small bowel investigation had a small bowel barium enema.

Results

Eighty-nine patients (36 men) of mean age 65 (range 35–84) years underwent BDE for investigation of iron-deficiency anaemia. There were no complications. The mean duration of the procedure was 25 min. Colonoscopy to the caecal pole was possible in 83 patients (93 per cent). Of the six 'colonoscopic failures', three were due to inadequate bowel preparation and three patients had a

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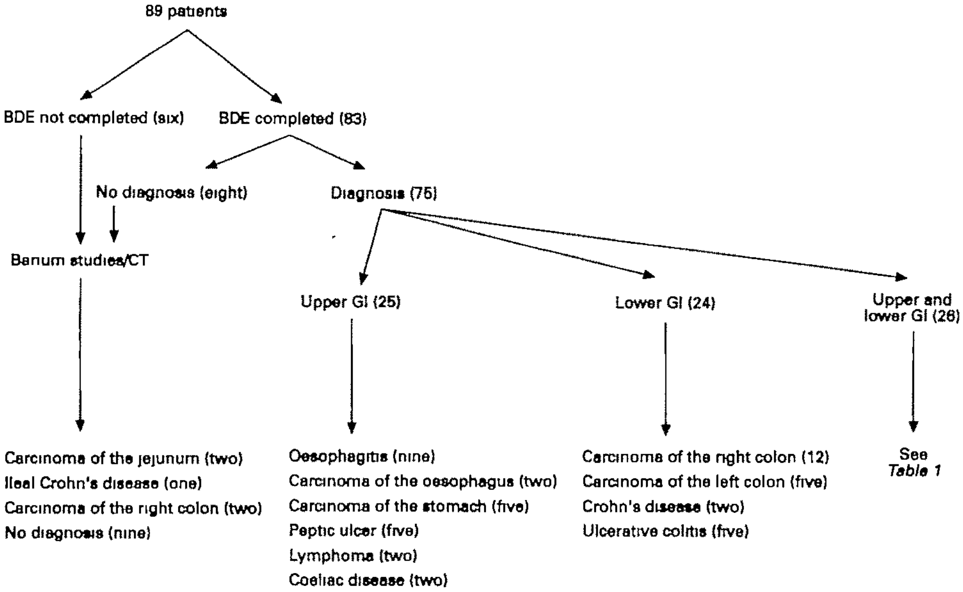

Fig. 1 Schematic diagram showing investigations and diagnosis in 89 patients with iron-deficiency anaemia. BDE, bidirectional endoscopy; CT, computed tomography; GI, gastrointestinal

Table 1 Endoscopic diagnosis in 26 patients with both upper and lower gastrointestinal pathology

	Oesophagitis	Barrett's ulcer	Peptic ulceration	Carcinoma of the stomach	Carcinoma of the ampulla	Total
Colonic polyps	4		3		1	8
Carcinoma of the right colon	11			1		12
Carcinoma of the left colon		1	1			2
Crohn's disease			1			1
Ileal carcinoid	1					1
Angiodysplasia	1			1		2
Total	17	1	5	2	1	26

Table 2 Details of 26 patients with oesophagitis

Oesophagitis	Upper GI pathology alone	Upper and lower GI pathology	Total
Grade II	4	13	17
Grade III	5	4	9
Total	9	17	26

GI, gastrointestinal

tortuous colon which did not allow visualization of the right colon.

Seventy-five patients (84 per cent) had a cause for anaemia established after BDE alone. Twenty-five patients (28 per cent) had upper gastrointestinal pathology alone, 24 (27 per cent) had colorectal pathology alone and 26 (29 per cent) had both upper and lower gastrointestinal pathology (*Fig. 1* and *Table 1*). In total, 26 patients had oesophagitis (*Table 2*), one had a Barrett's ulcer, ten had peptic ulceration and twelve had upper gastrointestinal malignancy. All 37 patients with upper gastrointestinal inflammation were treated medically and all patients with malignancy had surgery. No patient developed recurrent anaemia after treatment. Two of 34 patients with a macroscopically normal upper gastrointestinal endoscopy had coeliac disease diagnosed by duodenal biopsy and were treated successfully with a gluten-free diet.

In total, 49 patients (55 per cent) had lower gastrointestinal pathology and one patient had an ileal carcinoid diagnosed colonoscopically. All 31 colon carcinomas were resected and no patient developed recurrent anaemia. Eight other patients had colonic polyps snared and removed. All were adenomas (one villous, six tubulovillous and one tubular) greater than 1 cm in diameter with signs of bleeding from the surface. There were two cases of angiodysplasia; one of these was in the right colon of a 58-year-old man who also had a node-positive gastric adenocarcinoma. He underwent total gastrectomy and made an uneventful recovery but 6 months later presented with recurrent anaemia and required a right hemicolectomy to control bleeding from the angiodysplasia. The other patient was a 79-year-old woman who presented with oesophagitis and right colon angiodysplasia. The anaemia continued despite healing of the oesophagitis and, as the patient was not fit for surgery, she has been treated with intermittent blood transfusions as required. Eight cases of inflammatory bowel disease were diagnosed endoscopically and all were treated successfully with appropriate medical therapy and the anaemia resolved.

Twenty-six patients (29 per cent) had pathology in both the upper and lower gastrointestinal tract (*Table 1*).

Eleven patients with right colon cancer had oesophagitis and another had gastric carcinoma. Except for the two patients with angiodysplasia dual pathologies were treated together and the anaemia resolved.

Twenty patients (22 per cent) had 21 non-endoscopic investigations (six barium enemas, 14 small bowel barium enema studies and one computed tomography). These yielded a diagnosis in five patients (*Fig. 1*). No cause for the anaemia was found in nine patients (10 per cent) all of whom, to the authors' knowledge, remained well on iron therapy 3–12 months after investigation.

Discussion

In this group of 89 patients with iron-deficiency anaemia, BDE found a cause in 75 (84 per cent). Other investigations yielded a diagnosis in five patients but no cause for the anaemia was found in 10 per cent (*Fig. 1*). In all but one patient, who had colonic angiodysplasia and was unfit for surgery, treatment of the bleeding pathology resolved the anaemia. The present result compares favourably with previous studies using this technique where sources of bleeding were found in 50 per cent[5] and 71 per cent[6] of patients.

It might be argued that by performing BDE on everyone, patients with upper or lower gastrointestinal pathology alone are subjected to unnecessary additional investigations If all patients with iron-deficiency anaemia who have a positive finding on upper gastrointestinal endoscopy undergo colonoscopy just over half will have an unnecessary colonoscopy (*Fig. 2*). It was not, however, possible to predict which patients would have positive findings on colonoscopy as their symptoms were non-specific. Indeed, this was an important criterion for inclusion in this study.

Previous studies, which have also included oesophagitis as a potential bleeding source, found dual pathology rates of 9–17 per cent but the severity of oesophageal inflammation was not entirely clear[1,5,6]. The higher rate (29 per cent) in the current series may result from inclusion of grade II oesophagitis. If grade II oesophagitis is excluded the incidence of dual pathology in this series is 15 per cent. Most clinicians would be reluctant to attribute anaemia to grade II oesophagitis without investigating the colon and, in support of this, 13 of 17 patients with grade II oesophagitis had colonic pathology, compared with four of nine with grade III oesophagitis. Therefore, if upper gastrointestinal endoscopy detects a bleeding source other than grade II oesophagitis there is a one in seven chance that there will be a second pathology in the colon. Detection of dual pathology is clinically important as illustrated by the patient with a node-negative gastric carcinoma and a right colon carcinoma who had a gastrectomy and right hemicolectomy. This patient remains alive and well after 3 years. It is always tempting to attribute the patient's anaemia to the first gastrointestinal lesion found and to proceed no further. This and previous studies demonstrate the importance of investigating both the upper and lower gastrointestinal tract in all patients with iron deficiency and non-specific symptoms.

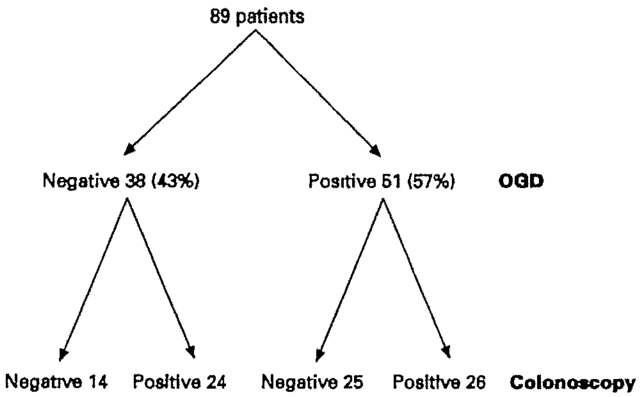

Fig. 2 Value of colonoscopy performed after positive or negative findings at gastroscopy OGD, oesophagogastroduodenoscopy

Fifty-one per cent of these patients had gastrointestinal malignancy compared with much lower rates in the other studies[5,6]. The reason for this is unclear but may reflect different referral patterns. General practitioners who suspect an underlying malignancy may be more likely to refer the patient to a general surgeon rather than a gastroenterologist. No symptom patterns, however, were detected to support this hypothesis.

For BDE to successfully diagnose causes of gastrointestinal blood loss it is important that colonoscopy be complete in a high percentage of cases. If the caecum cannot be reached a barium enema must be performed; two of the six patients in whom colonoscopy failed in this series had right colon cancers discovered at subsequent barium enema. If endoscopy is normal and duodenal biopsy has excluded coeliac disease a small bowel barium study would seem prudent as two cases of jejunal carcinoma were unexpectedly detected in this way. Enteroscopy is probably more accurate at finding small bowel bleeding sites than barium studies[8] but it is not widely available. Perhaps its use might have detected small bowel ulceration in some of the nine patients in whom a bleeding source was not found.

In conclusion, synchronous BDE is an effective investigation for patients with iron-deficiency anaemia. It found a cause for blood loss in 84 per cent of patients after a single visit to the endoscopy unit and resulted in successful treatment of the anaemia. Dual pathology was common and malignancy accounted for 51 per cent of diagnoses. Thorough investigation of iron-deficiency anaemia is important and the routine use of synchronous BDE is a successful way of ensuring this.

Acknowledgements

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Randomized controlled trial of open and closed haemorrhoidectomy

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Background This study was a prospective randomized comparison of healing following open and closed haemorrhoidectomy.

Methods Sixty-seven consecutive patients (mean(s.e.m.) age 45(1·7) years; 35 men, 32 women) with three prolapsed piles were randomized to open haemorrhoidectomy ($n = 34$) or closed haemorrhoidectomy ($n = 33$).

Results Mean(s.e.m.) follow-up was 8·7(0·2) months. There were no differences in the linear analogue pain scores, analgesic requirements and length of hospitalization after open haemorrhoidectomy and closed haemorrhoidectomy. Complete wound healing took significantly longer after closed haemorrhoidectomy (mean(s.e.m.) 6·9(0 7) weeks) compared with open haemorrhoidectomy (4·9(0·4) weeks) ($P < 0{\cdot}05$). This was related to wound dehiscence in eight patients. Complication rates, however, were similar except for prolonged serous discharge from unhealed wounds. The anal manometry findings after both procedures were equivalent.

Conclusion Open haemorrhoidectomy leads to faster and more reliable wound healing, although this did not result in less pain or fewer complications.

It remains uncertain whether haemorrhoidectomy wounds heal better by granulation or following primary repair. Open haemorrhoidectomy allows free wound drainage which may reduce infective complications[1]. Closed haemorrhoidectomy may heal more rapidly[2]. This study aimed to compare these two techniques. All patients required excision of three prolapsed, irreducible piles. Both operations were performed using diathermy excision techniques[3].

Patients and methods

Sixty-seven consecutive patients with three irreducible haemorrhoids were recruited with consent, over 6 months They were 35 men and 32 women, with a mean(s.e.m.) age of 45(1·7) years. Thirty-four had open haemorrhoidectomy and 33 closed haemorrhoidectomy. Surgery was performed under general anaesthesia in 42 patients (63 per cent) and caudal anaesthesia in 25 (37 per cent) There were no significant differences in the age, sex and anaesthesia method between the open and closed haemorrhoidectomy groups.

Haemorrhoidectomy techniques

Both techniques were performed in the lithotomy position.

The technique of open haemorrhoidectomy has previously been described elsewhere[3,4]. The piles were excised using a diathermy without ligation of the pedicles. An Eisenhammer anal retractor allowed visualization of dissection to the anorectal junction Subsequently the wounds were left open to granulate.

Closed haemorrhoidectomy was done through an Eisenhammer anal retractor; the piles were excised to the anorectal junction with diathermy. The base of the pedicle was transfixed with 3/0 polyglactin[2] The edges of the haemorrhoidectomy wound in the anoderm and skin were sutured with continuous polyglactin. During closure, small bites of the internal sphincter were included to fix the anoderm to the anal canal.

Anal dilatation was not done The anal canal was not packed in either open or closed haemorrhoidectomy groups. After operation, the care was similar with Sitzbaths, fibre supplements, laxatives, and analgesia on demand

Assessment

The pain score was assessed by an independent blinded observer (M T) A linear analogue scale was used, where 0 represented no pain and 10 represented the worst pain ever experienced[3]. The pain score was taken on the first postoperative day, and repeated daily for 1 week. The latter was done by telephone after discharge. Outpatient follow-up continued weekly until the wounds had completely healed. Wound healing was observed by spreading the buttocks apart and confirmed by insertion of a small anoscope well lubricated with lignocaine gel. Wound dehiscence was defined as any gaping of the wound whether in the anal canal or perianal skin. Anal manometry was performed using a microcapillary perfusion system[5] (Synectics, Stockholm, Sweden).

Statistical analysis was performed using the χ^2, Wilcoxon and Mann–Whitney tests where appropriate.

Results

There was no difference in the time taken to perform open haemorrhoidectomy (mean(s.e.m.) 9·1(0·7) min) or closed haemorrhoidectomy (10(0·9) min). The postoperative pain scores and analgesia requirements are shown (*Table 1*). No differences were observed between the two groups. Patients who had undergone open haemorrhoidectomy had their first postoperative bowel movement slightly earlier (median 1 (range 0–2) day after operation) than the patients undergoing closed haemorrhoidectomy (median 2 (range 0–3) days) ($P < 0{\cdot}001$). However, this did not affect their length of hospitalization (open haemorrhoidectomy median 2 (range 1–4) postoperative days; closed haemorrhoidectomy 1·5 (range 1–12) postoperative days). There were no differences in the complications after open and closed haemorrhoidectomy (bleeding: open haemorrhoidectomy, two; closed haemorrhoidectomy, three; faecal impaction: open haemorrhoidectomy, three; closed haemorrhoidectomy, none). All bleeding after haemorrhoidectomy was secondary in nature, occurring at a mean(s.e.m.) 9·6(2·8) days after surgery.

On follow-up, the wounds sustained at closed haemorrhoidectomy were completely healed more slowly (mean(s.e.m.) 6·9(0·7) weeks after operation) than the

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Table 1 Pain after open and closed haemorrhoidectomy

	Open haemorrhoidectomy ($n=34$)	Closed haemorrhoidectomy ($n=33$)	P
Postoperative pain score during first 24 h	5 (1–8)	5 (2–8)	1
Maximum postoperative pain score	5 (3–9)	6 (2–8)	0·6
Pain score at first postoperative bowel movement	4 (0–9)	4 (0–8)	0·3
Ketoprofen requirements (100 mg tablets)	4 (1–12)	2 (2–12)	0·4
Pethidine requirement (1 mg per kg body-weight intramuscular)	0 (0–3)	0·5 (0–3)	0·3

Values are median (range). Pain score 0, no pain; 10, worst pain ever experienced χ^2 test showed no significant differences between the two groups

open haemorrhoidectomy wounds (4·9(0·4) weeks) ($P<0·05$). This was caused by eight patients who had wound dehiscence after closed haemorrhoidectomy. Serous discharge was present until these wounds healed after 8–16 weeks. There were no differences in the anorectal physiology findings between the open and closed haemorrhoidectomy groups, either at 6 weeks or 3 months after surgery.

Discussion

This study compared wound healing rates after open and closed haemorrhoidectomy. Closed haemorrhoidectomy wounds took longer to heal completely (7 weeks) than wounds sustained using the open haemorrhoidectomy technique (5 weeks). Primary repair should lead to earlier healing[2,6] but this was not realized because of the wound dehiscence in eight of the 33 patients who underwent closed haemorrhoidectomy. Wound dehiscence has been reported in up to 50 per cent of patients after closed haemorrhoidectomy[7]. Postoperative pain was similar for the two techniques (although the estimated power for this was 60 per cent), consistent with a previous study comparing submucosal *versus* open haemorrhoidectomy[8]. Other complication rates were also similar, with incidences comparable to those of previous reports[3,9–11].

Where injury to the internal anal sphincters is avoided, postoperative reduction in anal pressures would not be expected following either technique. No significant differences were observed in operating time or hospitalization. The open haemorrhoidectomy technique, however, was simpler and did not require any extra effort in suture application. It is arguable whether wound dehiscence would be as likely if closed haemorrhoidectomy was performed on fewer than three piles or if the haemorrhoidal tissue excised was less. The tissue tension under such circumstances might have been less likely to have resulted in dehiscence. In this study, however, there was little to choose between techniques although healing was significantly quicker after open haemorrhoidectomy.

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Population-based audit of colorectal cancer management in two UK health regions

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Background To obtain information on the contemporary management of colorectal cancer in the UK to assist in the development of management guidelines, an independent, 1-year population audit was carried out in Trent Region and Wales.

Methods Data were collected on all patients admitted to hospital with a new diagnosis of colorectal cancer in a 1-year period.

Results Of 3520 patients, 3221 (91·5 per cent) had surgery. Emergency/urgent operations were carried out as the first procedure in 552 (17·1 per cent). Resection of the primary disease was achieved in 2859 (81·2 per cent) and this was deemed curative in 2070 (58·8 per cent). Twenty-one per cent of all patients had metastatic disease at presentation. Overall, 30-day operative mortality was 7·6 per cent (21·7 per cent for emergency/urgent and 5·5 per cent for scheduled/elective procedures). Anastomotic dehiscence occurred in 105 patients (4·9 per cent); this was 3·9 per cent after colonic resections and 7·9 per cent after anterior rectal resections. Elective rectal excision resulted in a permanent stoma in 486 of 1054 patients (46 per cent).

Conclusion This initial report from a comprehensive, independent audit of colorectal cancer management shows improvement in some aspects of treatment as evidenced by improved anastomotic dehiscence and stoma rates when compared with previous studies. However, there has been little improvement in the proportion of patients presenting with advanced disease, and curative resection rates remain low.

Colorectal cancer is the second most common cause of cancer death in westernized countries after lung cancer[1]. Cancer registry data from 1987 record about 28000 new cases and 19000 deaths in the UK[2–4]. Between 1961 and 1986 there has been little change in death rates[5], and there is considerable scope for improving the results of treatment. It is not clear, however, whether this can be achieved by raising the standards of existing therapeutic strategies, or whether it will be necessary to await the development of radically new and better approaches to the disease.

There is evidence to suggest that wide variations exist in the outcome of surgical treatment. Between 1976 and 1980 the Large Bowel Cancer Project examined 1466 patients undergoing surgical resection and anastomosis, and found that the anastomotic leakage rate for individual surgeons varied from 0·5 to 30 per cent[6]. The same project showed a variation in local recurrence rates from less than 5 per cent to greater than 20 per cent amongst surgeons who had carried out 30 or more resections[7]. Similarly, McArdle and Hole[8] found variations of 0–25 per cent for anastomotic leakage rates, 8–30 per cent for postoperative mortality, and 0–21 per cent for local recurrence rates amongst 13 surgeons operating in a single hospital between 1974 and 1979.

Given this degree of variation, it is conceivable that standardizing treatment at an acceptable level could improve overall results. One way of achieving this might involve the production of appropriate guidelines, but, to be effective, these must be based on firm evidence from the literature[9,10]. In terms of outcomes, however, while the literature contains the 'gold standards' at which to aim, it is important that standards set by guidelines should be achievable.

Thus, when the Department of Health approached the Royal College of Surgeons of England in 1991 for guidelines on the management of colorectal cancer, it was decided that a comprehensive, population-based audit was required to provide contemporary information on presentation, management and outcome in large bowel cancer. Previous audits of colorectal cancer management have been performed, with the Large Bowel Cancer Project being the best known and most comprehensive study of this type. However, it is more than 15 years since data collection for this project ceased, and it was based on a select group of interested surgeons. In this paper, we present the initial results of an independent, population-based audit of all patients presenting to hospital with a diagnosis of colorectal cancer in Trent Region and Wales.

Patients and methods

An expert working party, set up by the Royal College of Surgeons of England, directed the study and agreed a data-collection pro forma. All surgeons treating colorectal cancer in Trent Region and Wales agreed to participate. In addition, all physicians, geriatricians, oncologists, pathologists, hospital chief executives and coding departments were informed of the study.

Six specially-trained research assistants collected data on all patients presenting with a diagnosis of colorectal cancer to all hospitals in Trent Region between July 1992 and June 1993, and in Wales between January and December 1993. Hospitals were visited in rotation by the research assistants, and all patients

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presenting since the previous visit were identified using a number of avenues including the hospital records systems, histopathology records, audit clerks and surgeons' secretaries. The case records, operation notes and histopathology reports were then reviewed, and the relevant data collected by means of a proforma. After completion, the form was checked by a single research fellow (J.M.), and the data transferred to a microcomputer by means of an optical reading scanner. The data were stored and analysed using the Statistical Package for the Social Sciences for Windows (SPSS, Chicago, Illinois, USA). All data were coded for reasons of confidentiality.

At the beginning of the study, the data collectors in both regions were given specimen patient records from which to abstract data, to check on conformity of interpretation The quality of the data throughout was maintained by regular meetings between the data collectors and the research fellow. Validation procedures consisted of a 10 per cent rate of random checks in which the data collected were compared with the original patient records

A questionnaire was sent to all participating surgeons asking them, among other questions, to declare their primary interest. The options provided were (1) coloproctology; (2) gastrointestinal surgery, (3) general surgery; and (4) some other interest.

Definitions

For the purposes of this initial report, the following definitions are used:

Operations. These have been classified according to the criteria used by the National Confidential Enquiry into Perioperative Deaths[11] as follows· (1) emergency: immediate operation, resuscitation simultaneous with surgical treatment; (2) urgent. operation as soon as possible after resuscitation; (3) scheduled: early operation, but not immediately life-saving; and (4) elective: operation at a time to suit both patient and surgeon

Tumour site The site of the primary tumour was determined by the description on barium enema or at operation. A rectal tumour was defined as being at or below 15 cm from the anal margin on sigmoidoscopy. Where measurements were not available, the operative or barium enema descriptions were used. Although the term 'rectosigmoid' is imprecise, it is in common use, and is used in this report to describe tumours which could not be defined as definitely rectal or sigmoid on the available data.

Tumour stage. The tumour stage was classified using Dukes staging on resected specimens[12], but including the term 'stage D' to denote distant metastases where appropriate

Curative resection. This was defined as removal of the primary tumour in which there was no macroscopic evidence of residual disease either locally or at distant sites

Operative mortality In-hospital death or death within 30 days of a surgical procedure.

Anastomotic dehiscence. Unequivocal clinical evidence of anastomotic breakdown with or without radiological confirmation.

Results

Trent Region consists of 11 health districts, Wales comprises nine and, during the study periods, there were 52 hospitals and 161 consultant surgeons (excluding locums) dealing with patients with colorectal cancer. In the study periods, a total of 3520 individual patients were admitted with newly diagnosed colorectal cancer. The combined population of Trent Region and Wales is 7603000, giving an overall colorectal cancer incidence of 46·3 per 100000. The disease is more common in Wales (52·8 per 100000) than Trent (42 per 100000). The number of patients coming under the care of individual consultant surgeons in the 1-year period varied from one to 98, with 24 surgeons seeing less than five cases per year (*Fig. 1*).

Tumour site

Cancer was located in the rectum in 32 per cent, colon in 58 per cent and rectosigmoid in 10 per cent. Distribution of tumours in the anatomical subdivisions of the colon is shown in *Table 1*. Tumours were multiple in 142 cases (4 per cent).

Tumour stage

In analysing tumour stage, the Dukes staging system was used. The majority of pathologists in the study used this system and, even when the stage was not stated explicitly, it was usually possible to derive it from the histology

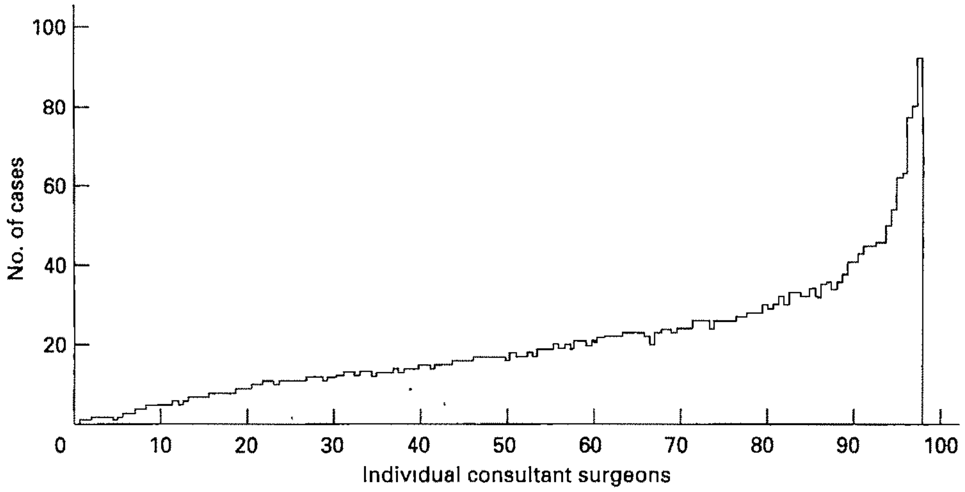

Fig. 1 Number of patients with colorectal cancer coming under the care of individual consultant surgeons in order of increasing number over a 1-year period

report. It was not possible to use the tumour node metastasis staging system, as very few reports contained sufficient detail.

Of 2859 patients in whom tumour resection was carried out, Dukes staging was available in 2625 cases (91·8 per cent). Reasons for absent stage data included inadequate information in 196 (6·8 per cent), resection for endoscopically excised lesions in which no residual tumour was found in four (0·1 per cent) and missing information in 34 (1·2 per cent). Distant metastases were present in 534 (19 per cent) of the resected cases and in 754 (21·4 per cent) overall; complete stage distribution is given in *Table 2*. For the purposes of classification, all locally-advanced tumours which were deemed inoperable were classified as 'D', even if there was no definite evidence of distant metastases. Tumours which were not resected for other reasons could not be staged ($n = 142$). There was striking variation between the districts in the proportion of tumours presenting at different stages, with the percentage with distant metastases varying from 17 to 31 per cent (*Fig. 2*).

It has to be accepted that the pathology data presented above is relatively 'soft' as its accuracy may vary according to the individual pathologist or laboratory. This is important as the results of surgical treatment are highly dependent on local tumour stage. In the context of an independent audit, however, such variation is inevitable and will be addressed separately. The presence of distant metastases is more reliable, however, although this too may be subject to variations in the intensity of investigation.

Table 1 Distribution of tumours in the anatomical subdivisions of the colon and rectum by individual patient

Site of tumour	No. of patients
Caecum	479 (14)
Ascending colon	239 (7)
Hepatic flexure	102 (3)
Transverse colon	137 (4)
Splenic flexure	103 (3)
Descending colon	171 (5)
Sigmoid colon	752 (21)
Rectosigmoid junction	361 (10)
Rectum	1125 (32)
Data missing	51 (1)
Total	3520

Values in parentheses are percentages. Tumours were multiple in 142 cases (4 per cent), but in most such instances the tumours were situated in the same part of the large bowel. When this was not the case, the worst Dukes stage was taken as the index tumour

Type of surgical treatment

Of the 3520 new cases, 3221 (91·5 per cent) had at least one operation, 2859 (81·2 per cent) underwent resection of the primary tumour, and 2070 (58·8 per cent) had a curative resection. The rate of curative resection varied from 54 to 76 per cent amongst the districts (*Fig. 3*), but there was an inverse correlation with the percentage of tumours presenting with distant metastases (Pearson correlation coefficient $-0·47$, $P = 0·04$). Of the initial operations performed, 552 (17 per cent) were emergency/urgent procedures, and 2608 (81 per cent) were scheduled/elective. In 61 patients it was not possible to ascertain the operation category.

Operative mortality

Overall operative mortality for all patients undergoing surgery was 7·6 per cent (246 of 3221). This was

Table 2 Stage distribution

	No of patients	
	All tumours	Resected tumours
Dukes stage		
A	281 (8)	281 (10)
B	1081 (31)	1081 (38)
C	729 (21)	729 (25)
'D'	754 (21)	534 (19)
No data	234 (7)	234 (8)
No resection (not 'D')	142 (4)	
No operation	299 (8)	
Total	3520	2859

Values in parentheses are percentages

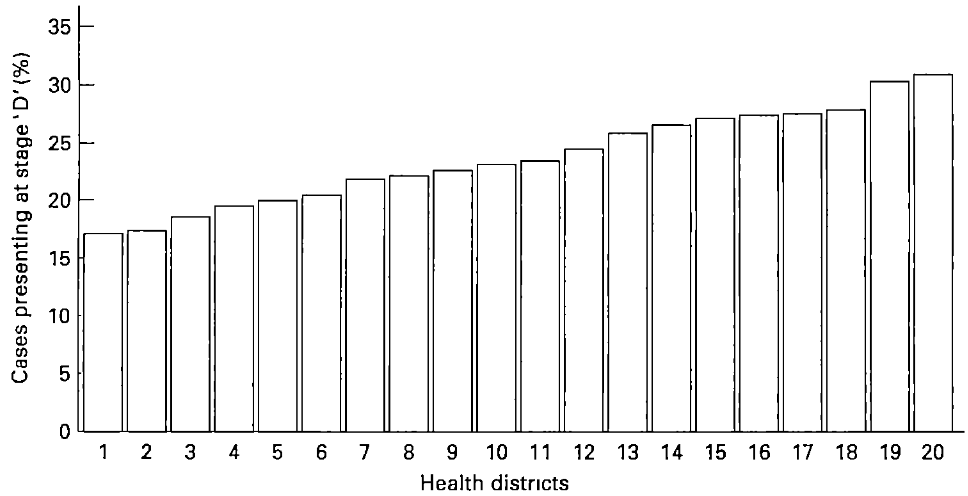

Fig. 2 Percentage of all patients presenting with distant metastases by health district

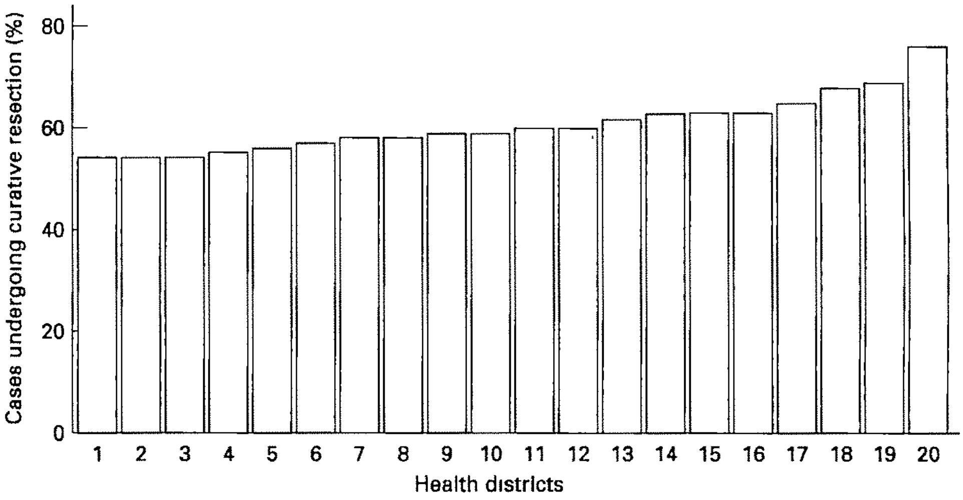

Fig. 3 Percentage of all patients deemed to have undergone curative resection by health district

influenced by category of operation and stage of tumour, with mortality being higher for emergency/urgent operations, palliative operations and operations for advanced disease (*Table 3*). It was also noted that although emergency/urgent operations were more likely to be associated with co-morbidity (as assessed by American Society of Anesthesiologists status and unfavourable tumour stage), subgroup analysis indicated that these factors did not account for the higher operative mortality (*Table 4*).

The operative mortality was also analysed by surgeon case volume and declared speciality interest. For the purposes of initial analysis, surgeons were grouped into categories according to the number of cases for which they had been responsible during the 1 year of the study. There was no significant association between specialization or case volume and operative mortality (*Table 5*). Further analysis taking mode of presentation and operation type into account again failed to reveal any differences.

Anastomotic dehiscence

There were 105 anastomotic leaks of a total of 2128 operations with an anastomosis, giving an overall rate of 4·9 per cent. This varied according to the site of the resected tumour, with rates of 3·9 per cent (61 of 1568) after colonic resections and 7·9 per cent (44 of 560) after anterior rectal resection. After anterior resection with defunctioning stoma, the leak rate was 8·6 per cent (9 of 105), which may reflect the more difficult nature of such operations.

Table 4 Operative mortality in emergency and elective operations by ASA status and Dukes stage

	Emergency/ urgent	Scheduled/ elective
ASA grade		
1	2 of 71 (3)	14 of 486 (3)
2	30 of 202 (15)	42 of 1153 (4)†
3	49 of 169 (29)	55 of 553 (9)†
4/5	29 of 53 (55)	14 of 59 (23)†
No data	9 of 57	18 of 357
Dukes stage		
A	1 of 13	8 of 259 (3)
B	30 of 174 (17)	33 of 897 (4)†
C	19 of 117 (16)	27 of 599 (5)†
'D'*	28 of 116 (24)	32 of 408 (8)†

Values in parentheses are percentages. *Resection only. †$P<0·001$. ASA, American Society of Anesthesiologists

Table 3 Operative mortality

Overall	246 of 3221 (7·6)
Emergency/urgent	120 of 552 (21·7)
Elective/routine	143 of 2608 (5·5)
Missing data	1 of 61
Curative operation	117 of 2108 (5·5)
Palliative operation	137 of 990 (13·8)
Equivocal operation	3 of 36
Missing data	7 of 87
Dukes stage	
A	9 of 281 (3·2)
B	64 of 1081 (5·9)
C	52 of 792 (6·6)
'D'	120 of 754 (15·9)

Values in parentheses are percentages

Table 5 Operative (30-day) mortality by consultant surgeon case volume and declared speciality interest

	Mortality rate	P
Case volume (in 1 year)		
≤ 10	26 of 270 (9·6)	
>10	238 of 3007 (7·9)	n.s.
≤ 30	156 of 2024 (7·7)	
>30	109 of 1496 (7·3)	n.s.
Speciality interest		
Coloproctology	36 of 462 (7·8)	
Gastrointestinal surgery	74 of 850 (8·7)	
General surgery	37 of 483 (7·7)	
Other	72 of 890 (8·1)	n.s.

Values in parentheses are percentages. n.s., Not significant

Stoma formation after elective rectal resection

Of 1054 scheduled/elective resections of the rectum, there were 560 anterior resections (53·1 per cent), 393 abdominoperineal resections (37·2 per cent), 93 Hartmann's procedures (8·8 per cent), and eight panproctocolectomies, giving an end-stoma formation rate of 46·8 per cent. Of the Hartmann's procedures, eight (8·6 per cent) were reversed during the study period so that the permanent stoma rate was 46 per cent. Of the 560 anterior resections, 105 (19 per cent) had temporary defunctioning stomas.

Discussion

This report describes the methodology and initial results of a completely independent, population-based audit of the current management of colorectal cancer in the UK. Previous published studies form the basis of our current understanding of the management of colorectal cancer in this country Foremost among these is the Large Bowel Cancer Project, in which data were collected between 1976 and 1980 on the patients with colorectal cancer of 94 surgeons in 23 hospitals in the UK[6,7]. This was a very detailed, comprehensive study, but was not population-based and involved a selected group of surgeons, many of whom were colorectal specialists. Furthermore, as surgeons were used as the source of patient data, it is conceivable that patients who were never seen by a surgeon could have been overlooked. The results also reflect practice 15 years ago.

In a more recent study 12 consultant surgeons prospectively collected information on 578 patients with colorectal cancer between May 1981 and July 1983[13,14]. However, this was also based on a selected population and again depended on interested surgeons willingly and actively collecting information.

McArdle and Hole[8] presented independently collected data on complications and outcome in 645 consecutive colorectal cancer patients between 1974 and 1976, and showed wide variations between the results of 13 individual surgeons. However, this study reflects practice in a single hospital 20 years ago, and although it has provided a seminal stimulus to investigate the variability of outcome, it cannot be regarded as representative of contemporary colorectal cancer management.

Cancer registries offer another source of valuable information, and provide the nearest approximation to the general picture in the UK[1]. In particular, data from the Birmingham registry have been scrutinized in some detail[15] and have shown only minimal improvement in results over a 25-year period. However, incomplete data capture and the retrospective nature of the documentation limit the conclusions that can be drawn from this type of study.

Trent Region and Wales embrace a wide range of different sizes and characters of hospitals and health districts, and the data are therefore likely to represent the UK as a whole. The overall incidence of colorectal cancer of 46·3 per 100000 is somewhat less than the 1987 national figure of 54·9[2–4], but this may reflect a low incidence in Trent. Distribution of cancers within the colon was similar to that found in the Birmingham Registry[16], as was the distribution of Dukes stage[15].

Given that the Trent/Wales audit is contemporary, accurate, comprehensive and representative, it is of particular interest to try to find if there have been any improvements in the immediate results of management compared with earlier studies. Clinical evidence of anastomotic dehiscence is a useful yardstick by which to measure the quality of surgery. The overall figure of 4·9 per cent is less than half the 13 per cent rate reported by the Large Bowel Cancer Project in 1980[6], although the resection and anastomosis rates were similar. Another important parameter, which may be related to quality of care and patient co-morbidity, is operative mortality. The overall figure of 7·6 per cent for Trent and Wales is less than the 11·8 per cent reported by the Birmingham Cancer Registry for the period between 1957 and 1981 However, it is similar to the 9 per cent for patients in the Large Bowel Cancer Study. It is clear that operative mortality is affected by patient fitness and tumour stage, but it does not seem to be influenced by surgeon speciality or workload. Perhaps, in this area at least, surgeon-related factors are overridden by patient-related factors, and this might partially explain the lack of improvement with time. Further case-mix analysis of the operative mortality data will be carried out when recurrence and survival data are mature.

Rates of abdominoperineal excision of the rectum (APER) are also of great interest as it is now evident that this operation can be safely avoided in many more patients than had previously been thought[17,18]. In Trent and Wales, 37 per cent of operable rectal cancers were treated by APER. This compares well with 74 per cent in the Birmingham Cancer Registry report, and 46 per cent for both rectal and rectosigmoid tumours in the more recent but more selective Large Bowel Cancer Project[18]. However, a further 9 per cent of rectal cancers were treated by Hartmann's procedure and, in view of the low rate of reversal in the study periods, it is likely that many of these patients will have a permanent stoma. Nevertheless, the permanent stoma rate in this study does indicate an improvement with time, and may reflect an increased awareness that the '5-cm rule' for distal clearance can be safely reduced[19].

Less encouraging are the data on stage of presentation and rates of resection. In the Large Bowel Cancer Project[7], 11·9 per cent of the resected tumours were Dukes stage A compared with the 9·8 per cent in Trent and Wales. Similarly, the resection rate of 81 per cent in the earlier study was higher than in Trent and Wales (81 per cent). The curative resection rate in Trent and Wales was 59 per cent compared with 55 per cent for the Large Bowel Cancer Project and 50 per cent in the Birmingham Cancer Registry.

In this analysis, therefore, it appears that there has been an improvement in the results of the management of colorectal cancer, in anastomotic leak rate and the formation of a permanent stoma after rectal excision. On the other hand, it is disappointing to find that almost 20 per cent of patients present with disease that is not amenable to resection, and that attempts at curative resection are unsuccessful in another 20 per cent.

The results of this audit from Trent Region and Wales must be regarded as preliminary. The overall short-term outcome measures described have been incorporated in the Royal College of Surgeons' Guidelines on the Management of Colorectal Cancer in order to provide rough benchmarks for assessing practice[20]. However, the crucial areas of hospital and surgeon variability cannot be addressed adequately until data on disease recurrence and survival become available We believe that premature comparisons of this nature must be resisted in order to prevent action being taken on the basis of mistaken conclusions.

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Review of 1198 cases of penetrating cardiac trauma

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Background This study was a clinicoforensic analysis of the prevalence and outcome of traumatic cardiac injuries in Durban.

Methods Between 1990 and 1992, 1198 patients sustained cardiac trauma. Seventy (6 per cent) reached hospital alive and 1128 (94 per cent) were taken directly to the mortuary. Seven hundred victims had suffered stab wounds, 494 gunshot wounds and four blast injuries. Gunshot injuries increased from 34 per cent in 1990 to 50 per cent in 1992. The mean(s.d.) age was 30·5(5·4) years and the majority (91 per cent) were men.

Results Thirty-five (50 per cent) of those who reached hospital alive died, including all four gunshot victims. Significant factors associated with survival were isolated injury, the presence of cardiac tamponade (univariate and multivariate analysis), right ventricular injury, single cardiac chamber injury and absence of pleural breach (univariate analysis alone). Delay in operative intervention was associated with a higher mortality rate. When analysing the patients who did not reach hospital alive, 202 (18 per cent) with tamponade due to an isolated stab wound were identified as a subset who might have been saved with prompt treatment.

Conclusion An increasing number of gunshot injuries in combination with delays in reaching hospital and in receiving treatment accounted for the high mortality rate in this unselected series.

The escalation of accidental and non-accidental trauma in South Africa has been referred to as the 'malignant epidemic'[1]. A 40 per cent decrease in stab wounds and a 400 per cent increase in gunshot wounds of the torso has been documented between 1983 and 1992 at King Edward VIII Hospital[2]. The nature and sequelae of cardiac injury in the era when stab injuries were common at this institution have been reported previously[3]. The original study documented hospital data only. The overall local prevalence of cardiac injury is unknown. The present study of penetrating cardiac injury at King Edward VIII Hospital has evaluated both clinical and forensic data to determine the magnitude of the problem.

Patients and methods

From the records of King Edward VIII Hospital and the medicolegal mortuary, all patients who sustained a penetrating cardiac injury during the 3-year interval 1990–1992 were identified. The mechanism and site of injury, presence of tamponade, haemothorax and associated injuries, condition on admission, and surgical and/or post-mortem findings were documented No patient received cardiopulmonary bypass In the group who did not reach hospital alive, exact volumes of pleural and pericardial collections were noted at autopsy. A collection of 100 ml or more was considered to indicate cardiac tamponade. Associated injuries were recorded in all groups. Comparisons between operative and post-mortem findings were made in patients who were treated but did not survive. Statistical cross-tabulations using χ^2 analysis, Fisher's exact test and unpaired Student's t test were performed to assess the significance of tamponade, pleural breach, associated injury and admission to intervention time, with respect to survival in the hospital groups. Multiple logistic regression was used to confirm the association between death and clinical predictors. P values of 0·05 or less were considered significant

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Results

A total of 70 patients reached hospital alive, of whom 35 (50 per cent) subsequently died. Thirty-seven patients had minimal signs of life or an unrecordable blood pressure on admission, 22 of whom died. The 35 non-survivors and a further 1128 victims had cardiac injury identified at autopsy performed at the medicolegal mortuary. Three groups were therefore reviewed, the hospital survivors ($n = 35$), patients who died despite treatment ($n = 35$) and those who did not survive to receive medical attention before death, the mortuary group ($n = 1128$).

For all 1198 patients the mean age was 30·5 (range 5–77) years and 1096 (91 per cent) were men. In the years 1990, 1991 and 1992 there were 410, 338 and 450 patients respectively who sustained a penetrating cardiac injury. The mechanism of injury is shown in *Fig. 1.* Of the total 1198 patients, 697 had suffered stab wounds, 403 gunshot wounds, 95 shotgun wounds and three blast-related injuries. A rise in firearm injuries and slight decrease in stab injuries was noticeable over the 3 years. Of the patients who reached hospital alive, 66 had stab wounds and only four had gunshot injuries; none of the latter survived. The site of cardiac injury is shown in *Table 1.* The right ventricle was most commonly injured followed closely by the left ventricle. The chamber least likely to be injured was the left atrium. In 30 patients the heart was totally disrupted because of a blast or high-velocity gunshot injury. Some 232 injuries were noted to penetrate one or more chamber. In 117 patients a haemopericardium was found without identifiable myocardial or coronary vessel injury.

The incidence of factors which have been associated with outcome in the hospital groups is detailed in *Table 2.* Right ventricular injury, which was three times more common than left ventricular injury in survivors, conferred a significant survival advantage. In the non-survivors and the mortuary groups there was little difference in the pattern of ventricular injury. Fifteen of the 35 non-survivors had more than one chamber injured whereas all 35 survivors had a single chamber wound.

In patients who survived to reach hospital, pleural breach was noted in four of 35 survivors and in 28 of 35 non-survivors and was a significant risk factor for death. In the mortuary group, pleural breach was noted in 1062 (94 per cent). In 184 there was haemothorax of greater than 1·5 litres. All 35 survivors had sustained stab wounds whereas of non-survivors, 31 had stab injuries and four firearm injuries. There were 631 stab injuries (56 per cent) in the mortuary group, 498 (44 per cent) firearm injuries and three blast injuries.

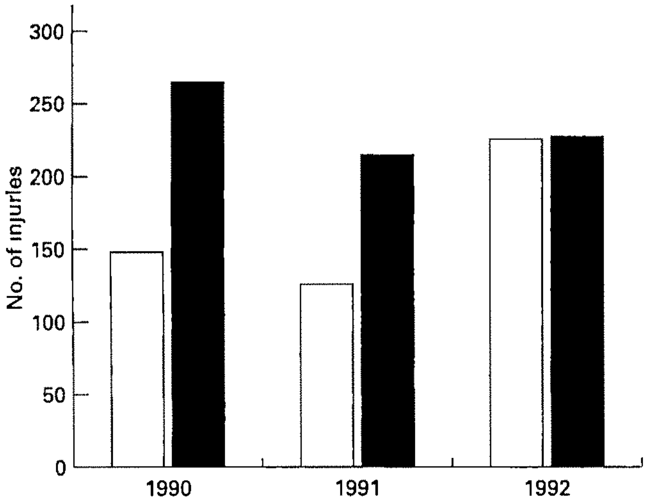

Fig. 1 Distribution of cardiac injuries by year and mode. ☐, Firearm injury; ■, stab wound

Table 1 Site of cardiac injury

	Right ventricle	Left ventricle	Right atrium	Left atrium
Survivors ($n = 35$)	25*	7*	0	3
Hospital non-survivors ($n = 35$)	12*	13*	8	25
Mortuary ($n = 1128$)	498	440	223	135
Total	535	460	231	163

*Right *versus* left ventricle, $P = 0{\cdot}018$ (χ^2 test)

The most common coronary vessel injury was the left anterior descending artery and occurred with almost equal frequency in the three groups; three of 35 in both the survivor and non-survivor groups and 101 (9 per cent) in the mortuary group. Coronary vessel injury had no significant impact on survival.

Cardiac tamponade was present in 32 of the 35 survivors, 20 of the 35 patients who died in hospital and 598 (53 per cent) of the mortuary group. The presence of tamponade significantly improved survival (*Table 2*). This was confirmed by multivariate analysis ($P = 0{\cdot}039$, odds ratio 6·0 (95 per cent confidence interval 1·1–30)).

Associated injuries were categorized by anatomical site: head and neck, lower torso, great vessels or extremity (*Table 3*). In survivors only one patient had an associated injury while 14 of the 35 patients who died after treatment had associated injuries. These included ten to the abdomen, three due to gunshot, one gunshot wound to the lung hilum necessitating pneumonectomy, and a patient with more than 20 stab wounds. In the mortuary group 708 victims (63 per cent) had an associated injury. Injuries to the head and neck, lower torso and great vessels occurred with almost equal frequency and extremity injuries were present in 10 per cent of victims. In 344 only one associated injury was present, in 198 there were two additional injuries, in 61 three, and in five all four anatomical sites were involved. Associated injury at a non-cardiac site was identified as a significant risk factor for death (*Table 2*). Multivariate analysis also confirmed this significance ($P = 0{\cdot}018$, odds ratio 0·073 (95 per cent confidence interval 0·008–0·639)). There was a 13·6-fold increase in mortality rate if an associated injury was present.

A comparison of operative with post-mortem findings identified seven missed injuries and four cardiac chambers misidentified. None of the victims had reaccumulated a pericardial collection.

In the majority of patients who were treated in hospital the delay between admission and surgery could be determined. Thirty-seven patients (67 per cent) had surgical intervention within 30 min of arrival at hospital, 12 (22 per cent) within 6 h and six (11 per cent) after 6 h. One patient was managed conservatively and survived. Those who had surgery within 30 min had a mortality rate of 38 per cent (14 of 37) compared with 72 per cent (13 of 18) for those operated on after 30 min or more. Some 202 (18 per cent) of the individuals who presented directly to the mortuary were thought to have had treatable injuries. Treatable patients were defined as those with cardiac tamponade, no associated injury and a wound inflicted by knife.

Table 2 Factors associated with outcome

Factor	Survival* ($n = 35$)	Death* ($n = 35$)	P	Odds ratio†
Right ventricle injury	25 (71, 56–86)	12 (34, 19–50)	0·002	4·8 (1·7–13·2)
Single chamber injury	35 (100)	20 (57, 41–74)	0·0001	
No pleural breach	31 (89, 78–99)	7 (20, 7–33)	0·0001	1·0 (9·6–100·6)
Stab injury	35 (100)	31 (89, 78–99)	n.s.	
Coronary artery injury	3 (9, 0–17)	3 (9, 0–18)	n.s.	
Not 'agonal'	20 (57, 41–74)	13 (37, 21–53)	n.s.	
Cardiac tamponade	32 (91, 82–100)	20 (57, 41–74)	0·001	8 0 (2·1–31·2)
Sole injury	34 (97, 92–100)	21 (60, 44–76)	0·0001	2·7 (4·5–115·3)

Values in parentheses are *percentage with 95 per cent confidence interval or †95 per cent confidence interval. n.s., Not significant

Table 3 Frequency of associated injury

	Site of associated injury			
	Great vessels	Lower torso	Head and neck	Extremity
Survivors ($n=35$)	0	1	0	0
Hospital non-survivors ($n=35$)	6	11	4	1
Mortuary ($n=1128$)	296	273	263	111
Total	302	285	267	112

Discussion

The number of patients with a penetrating cardiac injury admitted to this hospital during the study is nearly 30 per cent less than previously reported[3]. There are two reasons for this First, the incidence of gunshot wounds to the torso has risen dramatically[2] with an inevitable increase in multiple injuries and, in instances of isolated cardiac trauma, more severe cardiac damage; both factors result in a significantly higher mortality rate[4–7]. Second, the mean injury to hospital time in the Durban metropolitan region is 2 h[2]. This, in combination with more severe injuries, results in fewer victims surviving to reach hospital. These data are similar to reports from another South African centre[4] and India[8]. In countries with more efficient prehospital services, despite a similar change in weapons from knives to guns, far more victims of cardiac injury survive to reach hospital[9,10].

Of those admitted to hospital delay in the time to surgical intervention also affects mortality rates[4]. In this study patients who had surgery within 30 min had a higher survival rate than those in whom surgery was delayed. The duration between injury and intervention is probably the single most important factor affecting survival[4,5,11,12]. Immediate transportation of a patient with a suspected cardiac injury, the 'scoop and swoop' principle[13], has won widespread acclaim. At present the local constraints of excessive trauma, inadequate prehospital and hospital facilities, and the vast distances to secondary or tertiary centres make this concept unattainable in KwaZulu/Natal.

Despite the pressure on casualty facilities and operating theatres resulting from the volume of trauma, an acceptable admission to intervention time of 30 min was achieved in 67 per cent of patients. The reason for delay in hospital is often doubt regarding the diagnosis. The present study confirmed the findings of other authors that procrastination is often fatal[14,15]. One survivor was managed successfully with neither operation nor aspiration and there are protagonists of this approach[16]. There was no delayed haemorrhage from clot lysis which is well documented for up to 3 weeks after cardiac injury[17,18]. Conservative management is only applicable in a select group of patients who remain clinically stable with subtle, if any, signs of tamponade and in whom a cardiac chamber has not been penetrated; a subset of patients which even the most sophisticated investigations cannot identify reliably[14] and in whom operative delay may result in death[8]. This approach is potentially more lethal than the occasional prompt negative pericardotomy in cases of doubt, a view also held by others[5,11,15].

The influence of tamponade on survival has been debated extensively in the literature[9,15,17]. While the risks of exsanguination are obvious the role of tamponade in 'buying time' is less clear. This study confirms the findings of most authors that tamponade significantly improves survival. Although Buckman *et al.*[19] found that tamponade was not an independent predictor of early survival, the majority of injuries in their study were inflicted by firearms, and isolated tamponade from a solitary wound is rare after firearm injury compared with stab injury. Pleural breach was evaluated as a risk factor on the assumption that such patients are more likely to exsanguinate than those with tamponade and the present data confirm this hypothesis. Coronary vessel injury did not have a significant effect with regard to outcome, there being almost the same incidence in each group.

No gunshot victim survived in this study and 50 per cent of direct admissions to the mortuary had sustained gunshot injuries. Of those with stab wounds, however, a potentially salvageable low-risk group (tamponade due to a single wound) comprising 202 victims never reached hospital. It is misleading for Velhamos *et al.*[5] to suggest that penetrating cardiac trauma is 'a relatively innocent injury' when five times as many victims with the most favourable injury were admitted directly to the mortuary rather than to hospital. Forensic data are essential when assessing severity of injury. These patients serve to highlight shortcomings in the delivery of health care in KwaZulu/Natal and confirm that there are areas inadequately served by the prehospital services.

The hospital mortality rate of 50 per cent in this series is high considering that the majority of patients had sustained single stab wounds, and is higher than the rate of 30 per cent reported from this centre previously[3]. Mortality rates in the literature vary between 8·5 per cent in a South African series[20] of a selected group of stab victims to 81 per cent in an unselected series from California[21] in which 61 per cent of the injuries were inflicted by firearms. A number of factors responsible for the high mortality rate have already been highlighted but a further explanation lies in how and when the patients were stratified[19–23] for the risk of death. Mortality rate relates to the number of victims considered agonal or critically unstable on presentation as defined by Saadia *et al.*[22] or with a cardiovascular respiratory score of less than 3 as defined by Buckman *et al.*[19] These classifications are difficult to apply to retrospective data[24] but the high percentage of agonal patients in this series is largely responsible for the high mortality rate.

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Lymphoma presenting as an intramuscular mass

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Background Resection of an intramuscular mass without tissue diagnosis can lead to unnecessary surgery

Method During a 4·5-year period 19 previously healthy patients referred with an undiagnosed soft tissue tumour were found to have intramuscular non-Hodgkin's lymphoma. In seven patients this was the only focus of disease (Stage I_E). Patients were treated with chemotherapy or radiotherapy alone or in combination.

Results After mean follow-up of 43 months all of the patients with stage I_E lymphoma are alive and disease free.

Conclusion Primary intramuscular non-Hodgkin's lymphoma has a good prognosis. The importance of a tissue diagnosis by needle core biopsy is emphasized.

Numerous conditions may present as an intramuscular mass and tissue diagnosis must precede resection in order to avoid inappropriate or unnecessary surgery. Between January 1991 and June 1995, 19 patients were shown to have non-Hodgkin's lymphoma on needle biopsy of a suspected sarcoma in an intramuscular mass.

Non-Hodgkin's lymphoma presents in extranodal tissue such as the gut, central nervous system, skin, salivary glands, gonads and thyroid in about 20 per cent of cases[1–4]. In large series between 0·1 and 6 per cent of lymphomas have been reported as arising in soft tissue and infiltrating skeletal muscle[1,2]. Patients with widespread lymphoma may have secondary infiltration of the musculoskeletal system and in such cases the prognosis is poor[5]. The outlook for patients presenting with a single focus of intramuscular lymphoma has not been clearly established but one would assume it to be comparable to that for patients with other early-stage extranodal sites. Some 10–15 per cent of patients with non-Hodgkin's lymphoma present with Ann Arbor stage I or II disease (*Table 1*) and at these stages there is no significant difference in survival between those with nodal and extranodal disease[6,7].

Table 1 Ann Arbor staging classification for lymphoma

Stage	Criteria
I	Involvement of a single lymph node region (I) or single extralymphatic organ or site (I_E)
II	Involvement of two or more lymph node regions on same side of diaphragm (II) or localized involvement of extralymphatic organ or site plus one or more lymph node regions on same side of diaphragm (II_E)
III	Involvement of lymph node groups on both sides of the diaphragm (III), which may be associated with localized extralymphatic involvement (III_E) or the spleen (III_S) or both (III_{SE})
IV	Diffuse or disseminated involvement of one or more extralymphatic organs or tissues with or without associated lymph node enlargement. Site defined by symbols.
A	No constitutional symptoms
B	Unexplained fever, night sweats, more than 10 per cent weight loss

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Patients and methods

Of the 19 patients with a solitary intramuscular lymphoma 12 were women and seven men, aged between 15 and 78 (median 57) years. Presentation was with a painless intramuscular mass: four on the chest wall, seven on an upper limb, six on a lower limb and two on the back. No patient had palpable lymphadenopathy; one had a palpable spleen. Diagnosis was made on the basis of a single needle biopsy (Tru-Cut, Travenol Laboratories, Thetford, UK) in 18 patients, one patient required two biopsies. There were 17 B-cell non-Hodgkin's lymphomas, 1 T-cell non-Hodgkin's lymphoma and one anaplastic lymphoma. All patients were fully staged according to the Ann Arbor system; seven had stage I_E, four stage II_E, four-stage III_E, one stage III_{SE} and three stage IV disease. One patient in the group who had experienced 'B' symptoms had stage III_E T-cell non-Hodgkin's lymphoma.

Patients with stage I_E disease were treated with radiotherapy in the first instance plus chemotherapy if the mass did not disappear completely; five of seven patients required chemotherapy. Patients with more extensive disease were treated with chemotherapy and additional radiotherapy to the intramuscular mass if necessary; eight of 12 needed both. Thus 17 of 19 patients required chemotherapy.

Results

Follow-up details are shown in *Tables 2* and *3*. The patients with stage I_E disease have been followed up for between 11 and 68 (mean 43) months. All showed a complete response to treatment, none has developed recurrent disease and there have been no deaths even though five of seven had histologically high-grade lymphoma. Of the 12 patients with multifocal disease, one has been lost to follow-up, four have died from lymphoma at a mean time of 12 months, and two are alive but with recurrent disease at 17 and 22 months. Only five patients with multifocal disease are alive and disease free at a mean follow-up of 20 months (patients 14–18; *Table 3*).

Discussion

Almost every intramuscular mass can be diagnosed accurately by needle biopsy[8]. Sufficient tissue is obtained for histological and immunohistochemical differentiation between sarcoma, lymphoma, carcinoma or benign tumour. Inappropriate biopsy techniques can be detrimental to prognosis[9].

Table 2 Details of patients with stage I_E disease

Patient no.	Sex	Age (years)	Site	Histology	Treatment	Follow-up
1	M	26	Back	B-cell non-Hodgkin's lymphoma	Radiotherapy	68 months; alive and well
2	F	42	Buttock	High-grade B-cell non-Hodgkin's lymphoma	Radiotherapy and chemotherapy	65 months; alive and well
3	F	57	Shoulder	High-grade B-cell non-Hodgkin's lymphoma	Radiotherapy and chemotherapy	63 months, alive and well
4	M	58	Back	High-grade B-cell non-Hodgkin's lymphoma	Radiotherapy and chemotherapy	29 months; alive and well
5	F	64	Thigh	B-cell non-Hodgkin's lymphoma	Radiotherapy	54 months; alive and well
6	M	35	Arm	High-grade B-cell non-Hodgkin's lymphoma	Radiotherapy and chemotherapy	13 months; alive and well
7	F	44	Buttock	High-grade B-cell non-Hodgkin's lymphoma	Radiotherapy and chemotherapy	11 months; alive and well

More than 80 per cent of adult patients with non-Hodgkin's lymphoma present with superficial lymphadenopathy[10]. Muscle involvement by lymphoma can occur in three different ways: by metastatic spread, direct extension from bone or lymph nodes and as a primary intramuscular lesion. The first two modes of presentation should not cause diagnostic difficulties particularly in the presence of 'B' symptoms. Presentation of a lymphoma as a primary intramuscular mass is rare[1–4] and the literature suggests that the majority of lymphomas which present in this way are non-Hodgkin's B-cell tumours[4], in keeping with the present data.

The prognosis of patients with non-Hodgkin's lymphoma depends on the Ann Arbor stage at diagnosis. Unlike Hodgkin's lymphoma multifocal disease at presentation is common[10]. When non-Hodgkin's lymphoma affects a single site the prognosis is favourable, with a 5-year survival rate for patients with stage I_E non-Hodgkin's lymphoma of 81 per cent after treatment[6]. Vincent[10] quotes a 5-year survival rate of 61 per cent for patients with high-grade follicular lymphoma treated with radiotherapy alone and 89 per cent after chemotherapy. A combined regimen of chemotherapy and irradiation provides a 94 per cent 5-year survival rate for patients with high-grade stage I and II disease[10]. No significant difference in survival has been demonstrated between nodal and extranodal disease for patients with stage I or II lymphoma[6,7].

Six of the 12 patients in this series with multifocal disease died or had recurrent disease within 2 years. The absence of local recurrence or disease progression in the patients with a primary intramuscular lymphoma (stage I_E) after a mean follow up of 43 months suggests that intramuscular tumours behave in the same way as other stage I non-Hodgkin's lymphomas in having a relatively good prognosis.

Primary intramuscular non-Hodgkin's lymphoma is a rare tumour with as good a prognosis as any other single-

Table 3 Details of patients with more than one focus of disease

Patient no.	Sex	Age (years)	Site	Stage	Histology	Treatment	Follow-up
8	F	68	Shoulder, axilla, pleura	II_E	High grade B-cell non-Hodgkin's lymphoma	Chemotherapy and radiotherapy	10 months; dead
9	F	66	Thigh, orbit	III_E	B-cell non-Hodgkin's lymphoma	Chemotherapy and radiotherapy	12 months, dead
10	F	50	Chest, skin, axilla	III_E	B-cell non-Hodgkin's lymphoma	Chemotherapy and radiotherapy	12 months; dead
11	M	54	Thigh, lung, skin	III_E	T-cell non-Hodgkin's lymphoma	Chemotherapy	13 months; dead
12	M	78	Chest, bone marrow, axilla, neck	IV	B-cell non-Hodgkin's lymphoma	Chemotherapy and radiotherapy	17 months, recurrent disease
13	M	57	Chest, mediastinum	II_E	B-cell non-Hodgkin's lymphoma	Chemotherapy	22 months; recurrent disease
14	F	65	Thigh, bone marrow	IV	B-cell non-Hodgkin's lymphoma	Chemotherapy and radiotherapy	6 months; alive and well
15	F	38	Forearm, axilla, supraclavicular fossa	II_E	B-cell non-Hodgkin's lymphoma	Chemotherapy and radiotherapy	15 months; alive and well
16	F	18	Shoulder, axilla	II_E	Anaplastic large cell	Chemotherapy	20 months; alive and well
17	F	15	Chest, bone marrow, intrathecal	IV	High grade B-cell non-Hodgkin's lymphoma	Chemotherapy and radiotherapy	22 months, alive and well
18	F	63	Forearm, retroperitoneum	III_E	B-cell non-Hodgkin's lymphoma	Chemotherapy and radiotherapy	36 months; alive and well
19	M	66	Shoulder, spleen	III_{SE}	High grade B-cell non-Hodgkin's lymphoma	Chemotherapy	Lost to follow-up

focus disease despite highly malignant morphology. Diagnosis should be made by core needle biopsy which can be performed under local anaesthetic in the clinic.

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Risk factors for locoregional recurrence of scar carcinoma

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Background Squamous cell carcinoma (SCC) arising from scar tissue is rare and has a higher rate of recurrence than SCC arising in sunlight-damaged skin. The risk factors related to locoregional recurrence in scar carcinoma were analysed retrospectively

Methods Ninety-one patients with SCC arising from scar tissue treated from January 1980 to January 1992 were studied. The following factors were evaluated using univariate and multivariate methods for locoregional recurrence: patient age, sex, tumour size, anatomical location, histological differentiation, cause of scar and regional lymph node dissection.

Results With a median follow-up of 30 months locoregional recurrence developed in 27 patients. The median interval to recurrence was 15 months. Sex ($P = 0{\cdot}0278$), tumour size ($P = 0{\cdot}0491$), and tumour grade ($P = 0{\cdot}0019$) were found to be associated with recurrent disease by univariate analysis, but on multivariate analysis only sex and tumour grade were risk factors for recurrence.

Conclusion Careful follow-up after treatment is recommended especially for female patients and those with high-grade tumours.

Scar carcinoma is a rare disease which arises in chronic fistulas, ulcers, and radiation-injured and burned skin[1–4]. Although the usual histology is that of squamous cell carcinoma (SCC), basal cell carcinoma, malignant melanoma and also sarcoma developing in scar tissue are occasionally reported[2,5–7]. Scar carcinomas have a poor prognosis compared with SCC arising in sunlight-damaged skin, for reasons which are unclear. In addition, recurrent disease carries a high mortality rate.

It is usually agreed that the phenomenon of scar carcinoma is associated with a mean latent period of chronic wounds of 30 years' duration[1,2,8–10]. However, the rapid development of SCC in scar tissue (acute scar carcinoma) has been reported[1,11,12]. Conversely, the mean interval from initial injury to the occurrence of SCC was lower in irradiated skin than in previously burned skin[8]. These tumours arise predominantly in the extremities. The distribution is in marked contrast to that of most sunlight lesions which are located in the head and neck[13].

Risk factors associated with locoregional recurrence were analysed previously in 1039 patients with SCC of the skin[14]. The results indicated that scar carcinoma was one of several risk factors. The present analysis concentrates specifically on scar carcinoma because of its different biological behaviour and because, to the authors' knowledge, there have been no multivariate analyses of clinicopathological risk factors associated with recurrence in patients with scar carcinoma.

Patients and methods

Between January 1980 and January 1992, 4265 consecutive patients with non-melanotic skin cancer were treated at Ankara Oncology Hospital Of these, 107 had scar carcinoma. Three patients who had basal cell carcinoma arising from scar tissue and ten in whom follow-up information was not available were excluded. Three patients who had lung metastases at time of diagnosis were also excluded from the study because they underwent chemotherapy and radiotherapy following surgery Thus, 91 patients diagnosed as having SCC who underwent primary curative surgery were studied.

Data were extracted from the patients' medical records and were accurately recorded and coded on a computer. These included age at diagnosis, sex, interval from time of initial cutaneous injury to the development of SCC, cause of initial injury, primary tumour size according to the tumour node metastasis (TNM) classification of the American Joint Committee on Cancer, degree of histological differentiation of the tumour, anatomical location, treatment modality, regional lymph node dissection, recurrent disease site, and time between treatment and locoregional recurrence.

Differences in the distribution of risk factors were determined using the χ^2 test. To examine the effects of more than one risk factor on locoregional recurrent disease, a stepwise logistic regression analysis was used. Backward elimination was performed, starting with all potential risk factors. For all tests, a P value of less than 0·05 was considered to be significant. The statistical analysis was performed by Statistical Package for Social Sciences (SPSS for MS Windows Release 5.0, Chicago, Illinois, USA)

Results

At the time of diagnosis, the mean(s.d.) age of the patients was 51(16) (range 15–78) years and the M:F ratio was 1·4:1. All the patients were white. The mean(s.d.) interval from initial cutaneous injury to diagnosis of SCC was 32(17) (range 1–72) years. The aetiology of the scars was as follows: burn scar (66 patients), radiotherapy (11) and osteomyelitis (14).

All the patients were treated with primary surgery. After operation locoregional recurrence occurred in 30 per cent of all patients with a median follow-up of 30 (range 9–109) months. Local skin recurrence developed in 20 patients. Regional recurrence (lymph node metastases) occurred in seven patients. No in-transit metastasis was encountered among these patients. The disease-free period varied from 4 to 94 (median 15) months.

Tumour location was grouped into four categories: head and neck (23 patients), trunk (13), upper extremity (13) and lower extremity (42). Primary tumour size (T) was classified according to the TNM classification: tumour

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2 cm or less in greatest dimension (T_1) in 13 patients; tumour greater than 2 cm but not more than 5 cm (T_2) in 19; tumour greater than 5 cm (T_3) in 50; and tumour invading deep extradermal structures (T_4) in nine patients. The majority (55 per cent) were T_3 tumours. The distribution according to histological differentiation of the tumour was as follows: well differentiated tumour (G_1) in 69 patients, moderately well differentiated (G_2) in 13 and poorly differentiated tumour (G_3) in nine patients.

Surgical treatment was determined by the extent of disease at diagnosis. A major extremity amputation was required to obtain tumour-free margins in 18 patients; others were treated with wide local surgical excision. In general, the defect was closed with a split-thickness skin graft or a random pattern flap.

Locoregional recurrence developed in 22 (30 per cent) of 73 patients treated with wide local excision and in five of 18 who underwent extremity amputation. The risk of locoregional recurrence was not affected by the type of surgical treatment ($P = 0{\cdot}8441$). No correlation was found between tumour size and development of recurrence in patients treated with wide local excision. However, a statistical difference was found in patients who underwent amputation. The relationship of these surgical treatment modalities and primary tumour size is shown in *Table 1*.

In addition to local excision or amputation, a concomitant regional lymph node dissection was performed as initial surgical management in eight patients who had suspicious adenopathy or lesions directly overlying regional nodal basins. All the lymph nodes removed were reactive. Cytological examination was not performed before regional lymph node dissection because no patient was found to have histologically proven metastatic lymph nodes. Furthermore, the risk of locoregional recurrence was not significantly different when comparing patients who did or did not undergo prophylactic regional lymph node dissection ($P = 0{\cdot}7621$).

Univariate analysis comparing patients who had recurrence with those who did not have recurrent disease showed a significant difference in patient sex ($P = 0{\cdot}0278$), tumour size ($P = 0{\cdot}0491$) and tumour grade ($P = 0{\cdot}0019$). Anatomically there was a preponderance of the carcinomas on the extremities, but there was no statistically significant difference between anatomical site and the development of recurrence ($P = 0{\cdot}4642$). The results of the univariate analysis are presented in *Table 2*.

The data were analysed further using the stepwise logistic regression model to investigate the risk factors for locoregional recurrence. At the final step, the variables tumour grade and patient sex remained (*Table 3*). Women had a higher risk of recurrence. The histological grade of the tumour was also significantly associated with locoregional recurrence. Poorly differentiated growths had a higher incidence of recurrent disease than well or moderately differentiated tumours. Univariate analysis showed a statistical difference in locoregional recurrence with increasing tumour size, but its relative predictive power has not heretofore been tested by multivariate analysis.

Table 1 Relationship between tumour size, surgical treatment and development of locoregional recurrence in 91 patients with scar carcinoma

Surgical treatment	Tumour size (T)*	*n*	No. with recurrence	*P*†
Local excision	T_1	13	2	0·20
	T_2	17	4	
	T_3	42	15	
	T_4	1	1	
Amputation	T_1	0	—	0·013
	T_2	2	0	
	T_3	8	0	
	T_4	8	5	

*Tumour node metastasis classification. †Pearson χ^2 test

Table 2 Univariate analysis of 91 patients with scar carcinoma

Variable	*n*	No. with recurrence	*P**
Age (years)			0·6977
≤40	31	10 (32)	
>40	60	17 (28)	
Sex			0·0278
M	53	11 (21)	
F	38	16 (42)	
Anatomical site			0·4642
Head and neck	23	9 (39)	
Trunk	13	3 (23)	
Upper extremity	13	2 (15)	
Lower extremity	42	13 (31)	
Cause of initial injury			0·2693
Burn	66	21 (32)	
Irradiation	11	1 (9)	
Osteomyelitis	14	5 (36)	
Primary tumour size (T)			0·0491
T_1	13	2 (15)	
T_2	19	4 (21)	
T_3	50	15 (30)	
T_4	9	6 (67)	
Histopathological grade (G)			0·0019
G_1	69	14 (20)	
G_2	13	7 (54)	
G_3	9	6 (67)	
Regional lymph node dissection			0·7621
No	83	25 (30)	
Yes	8	2 (25)	

Values in parentheses are percentages. *Pearson χ^2 test

Discussion

Scar carcinoma is a rare entity. Nancarrow[15] reported that the incidence of cicatrial cancer was 1·2 per cent[15]. In this series, scar carcinoma was encountered in 2·5 per cent of all the patients with non-melanotic skin cancer.

In general, SCC developing from scar tissue is considered to be an aggressive tumour with a high potential for local recurrence and metastasis. Although the exact reason for its aggressive behaviour is unknown, some authors have suggested that it is because the tumour originates from an 'immunologically privileged site'[16,17].

Table 3 Final regression model

Factors	*β*	Standard error	Exp (*β*)	*P*
Female	1·2638	0·5308	3·5387	0·0173
Grade 2 tumour	1·6050	0·6670	4·9777	0·0161
Grade 3 tumour	2·3537	0·8180	10·5240	0·0040

Model χ^2 17·716; log likelihood −90·874

Bostwick *et al.*[16] reported that six patients with scar cancer underwent adequate local excision and that locoregional relapse developed in all cases within 6 months following the treatment. In contrast, Bowers and Young[18] recorded that no recurrent disease developed in nine patients with SCC arising in burn scar, osteomyelitis or fistula. In this study, locoregional recurrent disease was seen in 30 per cent of 91 patients with scar carcinoma within a median interval of 15 months.

Arons *et al.*[2] reviewed 56 cases of skin cancer arising in burn scar, chronic leg ulcer, traumatic wound, chronic osteomyelitis sinus or fistula and pointed out that burn scar carcinoma showed aggressive behaviour, especially when arising on the extremities. According to their series the overall recurrence rate was 30 per cent and female patients had a higher recurrence rate than men (36 *versus* 29 per cent). Horton *et al.*[5] advocated that scar carcinoma on the extremity had a better prognosis than that on the trunk and face. The present study demonstrated that female sex was associated with an increased risk of recurrence, but no statistical significance was found for tumour location. In the present analysis there was no significant association between scar cause and recurrence, although Edwards *et al.*[8] noted that the recurrence rate was higher for SCC arising in irradiated skin than in burned skin (70 *versus* 52 per cent).

In this study, moderately well differentiated and poorly differentiated tumour was related to an increased risk of recurrence of 4·98- and 10·52-fold respectively compared with well differentiated tumour, although this result conflicts with a previous report[19]. The use of prophylactic lymph node dissection (PLND) remains controversial. Some authors suggest that PLND should be performed routinely if the lesion is histologically high grade[5,19,20] whereas others recommend it for locally advanced disease only[8,21]. Hejna[22] pointed out that inguinal nodal biopsy was negative in all seven of 19 patients in whom this was performed. Notwithstanding, four of his seven patients underwent radical groin and iliac lymph node dissection and no tumour was found in two patients.

In the present series, PLND was performed in eight patients without previous cytological examination or nodal biopsy. No patient was found to have histopathological lymph node metastases. Moreover there was no significant correlation between PLND and recurrence. Currently the present authors do not favour PLND, regardless of tumour grade and primary lesion size; their retrospective experience suggests that nodal biopsy should be performed if the patient has suspicious lymph nodes and that lymph node dissection should be performed only if the patient has histologically confirmed nodal metastases.

Amputation has been proposed as the appropriate treatment of choice, especially for high-grade tumour[8,21]. This study demonstrated that amputation was not superior to wide local excision. It should be noted that amputation should be required to obtain tumour-free margins for T_4 tumours only, regardless of the degree of tumour differentiation.

In conclusion, local surgical excision may be sufficient for local tumours. However, an aggressive surgical approach is required for locally advanced tumours. Careful follow-up after adequate surgical therapy is recommended particularly for women and those with high-grade tumours.

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British Journal of Surgery 1997, **84**, 1747–1752

Correspondence

The Editors welcome topical correspondence from readers relating to articles published in the Journal. Letters should be no more than 250 words in length and should be typed on A4-sized paper in double-spacing.

Role of endotoxin and nitric oxide in the pathogenesis of renal failure in obstructive jaundice

Sir

The role of the endothelium in the mediation of renal dysfunction in obstructive jaundice may be more complex than conceived by Dr Inan and colleagues (*Br J Surg* 1997; 84: 943–7). They proposed that the overproduction of nitric oxide could give rise to endothelial damage, the latter, in turn, leading to loss of endothelium-dependent guanosine 3′,5′-cyclic monophosphate (cGMP)-mediated vasorelaxation, with consequent renal hypoperfusion and renal dysfunction. The alternative model describes the synthesis of endothelin 1, a vasoconstrictor polypeptide[1], which is produced in excessive amounts by renal papillary tissue, in the presence of obstructive jaundice[2]. Increased blood levels of endothelin lead to renal arterial vasoconstriction, with consequent decrease in glomerular filtration rate, the latter having been shown to be reversible following administration of the endothelin receptor antagonist, bosentan[2]. In theory, vasodilators, such as nitric oxide, inhibit production of endothelin 1 through a common mechanism involving generation of cGMP[1]. The overproduction of nitric oxide documented by Dr Inan and colleagues might, therefore, be a manifestation of this defence mechanism, the latter possibly having been overwhelmed by an even greater endothelial synthesis of endothelin 1, in patients who subsequently experience renal vasoconstriction and renal failure. The defining characteristic of renal dysfunction in obstructive jaundice may be an imbalance between production of nitric oxide and renal papillary synthesis of endothelin.

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Herniography for groin pain of uncertain origin

Sir

We read with interest the article by Mr MacArthur and colleagues (*Br J Surg* 1997; 84: 684–5). We have also been evaluating herniography as a diagnostic technique for chronic groin pain of uncertain aetiology. Over an 18-month period 12 male patients with a mean age of 42 (range 15–72) years have undergone herniography. Strict indications were a history of groin pain for at least 6 months and a normal clinical examination, based on the report by Badruddoja *et al*[1] who demonstrated that 92 per cent of such patients have occult hernia.

To date, only one of the 12 patients had radiological evidence of a hernia which corresponded to the area of pain. Two patients had hernias demonstrated which did not explain their symptoms: one had an inguinal hernia on the opposite side, and the other had a tiny gluteal sac. Consequently, in 11 of 12 patients the investigation was of doubtful benefit as it did not alter management. One patient had a severe vasovagal attack with bradycardia and required overnight hospitalization, a recognized complication[2]; the herniogram was abandoned and this patient has not been included in our figures.

Although these numbers are small, our results so far do not support those of other series[1–3], which describe sensitivity rates of between 33 and 90 per cent[3]. In our practice, patients who have suspected inguinal hernia on clinical examination invariably are found to have one at operation. We wonder whether herniograms are being performed too readily on patients with cough impulses as this would explain the high sensitivity rates. We feel that our sensitivity rates are unlikely to alter significantly with greater numbers. Consequently, we question the benefit of herniography in chronic groin pain when the clinical examination is normal.

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Comparison of three operations for typhoid perforation

Sir

I wish to congratulate Dr Ameh and colleagues (*Br J Surg* 1997; 84: 558–9) on their attempt at tackling the difficult problem of typhoid enteric perforation (TEP). The mortality rates for the various techniques were high, i.e. 50 per cent for simple closure, 62 per cent for wedge excision and 36 per cent for segmental resection.

TEP is an intestinal complication of a systemic disease in which there is depression of immunity, fluid and electrolyte depletion and endotoxaemia. Attention must not, therefore, be concentrated entirely on the perforated bowel. By strict adherence to guidelines[1] we have been able to reduce the mortality rate for typhoid perforation to 6 per cent. These guidelines include early aggressive resuscitation, early limited surgery, thorough peritoneal lavage, instillation of 1 g of ampicillin into the peritoneum, fresh blood transfusion, and metronidazole[2] in addition to conventionally used chloramphenicol. TEP should be classified in four stages: stage 0, typhoid fever with no clinical or radiological evidence of perforation, stage 1s, typhoid fever with mild peritonism but no radiological or operative evidence of perforation, stage 1, localized peritonism with a single perforation but minimal peritoneal soiling, stage 2, mild peritonitis with one or two perforations and mild peritoneal soiling; stage 3, one or more perforations with moderate peritonitis; and stage 4, one large perforation or numerous perforations and abscesses and faecal contamination with friable loops of bowel matted together with pus in the paracolic gutters.

Three important factors determine the prognosis: the immunological status of the patient, the virulence of the organism, and the time of presentation[3,4]. It is therefore unrealistic to prescribe one particular operation for all patients as they may present in various stages.

The use of a two-layer anastomosis for closure of a perforation confers no advantage and might lengthen operating time. I use a single-layer seromuscular continuous 3/0 chromic catgut suture and have never experienced an anastomotic leak.

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Male breast cancer

Sir

Messrs Memon and Donohue (*Br J Surg* 1997; 84: 433–5) mention the epidemiology of male breast cancer, but ignore some interesting variations. In Eastern Africa 30 years ago male breast cancer was common Linsell[1] found an incidence of 11·6 per cent. At that time carcinoma of the breast (both sexes) was the fifth or sixth most frequently observed cancer, with a relative frequency of 5 per cent[2]. Now, 30 years later, carcinoma of the breast is a common condition in African women, exceeding carcinoma of the cervix in relative frequency. Carcinoma of the male breast is relatively rare.

While the relative rarity of cancer of the female breast was attributed to early child bearing, multiparity and lactation, the prevalence of cancer of the male breast was thought to result from high oestrogen levels, caused in turn by malnutrition and liver disease.

These theories have not been tested by formal epidemiological studies and it may be that their investigation would throw light on the pathogenesis of the disease.

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Improving the preoperative assessment of varicose veins

Sir

We agree with Mr Singh and colleagues (*Br J Surg* 1997; 84: 801–2) that there is a need to assess accurately patients with varicose veins to reduce recurrence rates. Their argument for the routine use of colour duplex scanning could be challenged. While colour duplex ultrasonography remains the gold standard, its use is not essential in every patient. Hand-held bidirectional Doppler ultrasonography (HHD) can be used to improve the accuracy of clinical examination and reduce the workload on the vascular laboratory and, hence, cost.

We have found HHD to be extremely accurate when assessing incompetence at the saphenofemoral junction with a sensitivity of 92 per cent and specificity of 94 per cent[1]. The technique fails in the assessment of the popliteal fossa and the deep venous system and cannot be relied on in these areas. As most patients presenting with varicose veins have saphenofemoral reflux only (66 per cent, Singh *et al.*; 50 per cent, Salaman *et al.*), a substantial number of patients can be assessed accurately using HHD and go straight to surgery. Arguments for 'routine' use of any investigative modality should always be considered with suspicion as this invariably leads to unnecessary investigations and increased costs. With intelligent use of a hand-held Doppler probe, the majority of patients with varicose veins can be assessed accurately in the clinic. Colour duplex scanning should be reserved for patients with refluxing signals in the popliteal fossa, a history of deep vein thrombosis or signs of chronic venous skin damage.

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Author's reply

Sir

There is no doubt that duplex scanning is the preoperative assessment of choice in patients with varicose veins. We agree with Messrs Salaman and Salaman that the resources necessary for routine duplex scanning are unlikely to be available within the NHS and reserved duplex assessment for patients with recurrent varicose veins, a history of venous thrombosis, signs of chronic venous insufficiency and clinical suspicion of saphenopopliteal reflux.

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Rectal cancer. The lessons of history and a prospective randomized trial

Letter 1

Sir

Mr Hainsworth and colleagues (*Br J Surg* 1997; 84: 652–6) reported results using total mesorectal excision (TME). They do not appear to have gained the principal advantage of TME (a low local recurrence rate) and have incurred a disadvantage (a high anastomotic leak rate). However, they should be applauded for reporting their experience for the true value of TME will only become apparent when others also report their experience.

The superior results often described by innovators of new surgical techniques are frequently not repeated when adopted by the wider surgical community. This is often because the original technique is subtley 'improved', and changes are already happending here. To avoid the high anastomotic leak rate associated with TME some surgeons are currently managing all but the lowest tumours with subtotal (more than 5 cm) mesorectal excision (SME). It is by no means clear that SME is the equal of TME and other variations in practice (e.g. washing out the rectum with a cytocidal solution) may influence results.

In the June issue, the *BJS* encouraged readers to only allow the introduction of new surgical techniques after critical evaluation, particularly within prospective randomized trials[1]. The case for such a trial of surgical technique in rectal cancer surgery could not be clearer and would be a good place for *BJS* readers to start

Heald's original suggestion was that TME removed any metastatic deposits that occurred by retrograde spread within the mesorectum distal to the tumour[2]. The rarity of extensive retrograde spread has been confirmed recently in two small contemporary studies and there is, therefore, evidence to suggest that SME should remove retrograde metastatic deposits as effectively as TME, but hopefully without the associated high anastomotic leak rate.

A further reason for a prospective randomized trial of rectal cancer surgery is that there appears to have been a subtle change in the underlying rationale for TME and greater emphasis appears to be being given to circumferential clearance, which is an integral part of both SME and TME, than to removal of the mesorectum more than 5 cm below the tumour. In 1910, Handley[3] wrote 'effective dissemination probably, as a rule, occurs through the mesorectum or peri-rectal tissue opposite the primary growth, and this is the tissue which requires most careful removal'. This encouraged Cheatle[4] to study the finding further and in 1914 he reported that by 'attempting to cut transverse sections of all the tissue in the majority of my cases I have not seen the sub-mucous spread greater than that seen in the extramural lymphatic distribution'.

The surgical and pathological principals that underlie the current rectal cancer surgery debate were recognized and documented many years ago The dominant figure in rectal surgery at that time was Miles and his observational reports (which also promoted the '5-cm rule') rather than these and later objective studies influenced rectal cancer surgery for most of this century. As a result contemporary surgeons and pathologists are relearning the lessons of history In this era of evidence-based medicine we need to ensure that rectal cancer surgery in the next century is based on science.

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Evaluation of a policy of total mesorectal excision for rectal and rectosigmoid cancers

Letter 2

Sir
I read with interest the article by Mr Hainsworth and colleagues (*Br J Surg* 1997; 84· 652–6). Much has been written on the advantages and complications of TME for rectal cancer. This article is correct in highlighting the use of TME for upper third and rectosigmoid cancers.

The use of TME for these proximal tumours may not be justified. Scott *et al.*[1] have shown that distal mesorectal spread can occur up to 3 cm beyond the main tumour mass. Distal mesorectal excision of 5 cm beyond the lower border of the tumour is therefore adequate in the upper third of the rectum, and this is the present practice of Karanjia and colleagues[2]. This should be a topic for a prospective randomized trial comparing local recurrence, 5-year survival rate and complications, in groups undergoing TME or 5-cm mesorectal resection for upper third rectal cancers.

There is less controversy about the use of TME for tumours of the mid rectum Adam *et al.*[3] have shown that lateral resection margin (LRM) involvement is associated with high local recurrence rates. Efforts should be directed towards developing imaging techniques to identify this subgroup before surgery. The effects of preoperative radiotherapy in reducing local recurrence could then be studied in this group.

When rectal cancer invades the anal sphincter abdominoperineal resection (APR) is inevitable. Patients with tumours treated by APR have had a poorer prognosis than those treated by anterior resection[4].

Morson (personal communication) noted that in most APRs the narrowest LRM was found at the level of the tumour. APR may produce inward coning producing a waist at the level of the tumour. The mesorectum cones down to and ends immediately above the levators. If TME is performed as part of APR this waist is produced. A resection that produces a constant diameter tissue cylinder around the rectum from the mesorectum through the levators to the anal verge might produce lower local recurrence rates. A trial comparing TME with the more radical resection would answer the question of which operation is best for these very low tumours.

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Author's reply

Sir
Messrs Aitken and Carter call for a randomized controlled trial to compare TME with SME in patients with proximal rectal cancers Is there a sound rationale for performing TME in proximal rectal cancer? Heald stresses the two principle components of TME· complete removal of the mesorectum down to the levator gutter, and precise dissection in the 'Holy Plane'[1]. Circumferential clearance has been shown to be arguably the most important marker of local curability. Data on the incidence of distal mesorectal deposits in rectal cancer are limited. Heald *et al.*[2] reported five patients from 113 undergoing anterior resections with distal mesorectal spread between 1 and 5 cm. Recent series report distal deposits in four of 20 patients, 1–3 cm below the tumour[3] and 12 of 50 patients, 2–5 cm below the tumour[4]. Heald *et al.*[2] reported in 1982 the practice of dividing the mesorectum at least 5 cm below the tumour for selected upper rectal cancer, yet still achieved remarkably low local recurrence rates.

The endpoints of a randomized trial would include local recurrence, survival and morbidity, especially leak, rate. If we assume a background local recurrence rate of 10 per cent, to detect a reduction to 5 per cent with a power of test of 80 per cent and α of 5 per cent would require study of 900 patients with proximal rectal cancer. With regard to leak rates, Aitken[5] reported a leak rate of 14 per cent with a policy of selected SME which is similar to our 16 per cent rate with TME. To detect meaningful differences in leak rates with the two techniques, large numbers of patients would be required As these principles of surgery are now widely practised, recruitment would probably prove extremely difficult. Many other surgeon- and patient-related variables exist and may well account for greater differences in outcome than this point of technique. These factors would make a randomized controlled trial very difficult to mount and further prospective, detailed pathological studies may yield more useful information.

Our paper did not address the choice of procedure for tumours of the lower third of rectum When sphincter-saving resections (SSRs) first became popular, there was concern that cancer clearance might be compromised. Very low tumours appeared to carry a higher risk of recurrence, but collected data from non-randomized series suggested that the outcome, tumour level for tumour level, was comparable for the two operations. Two groups report rates of LRM positivity in patients undergoing SSR and APR[6,7]. Although the data are uncontrolled, LRM positivity for APR *versus* SSR was 39 *versus* 17 per cent[6] and 21 *versus* 8 per cent[7]. APR does not appear to avoid the problem of LRM positivity and the lowest local recurrence rates reported have come from single surgeons practising very low anterior resection.

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Genetic instability in patients with metachronous colorectal cancers

Sir

I read with interest the article by Dr SenGupta *et al.* (*Br J Surg* 1997; 84 996–1000). I agree with the authors that the ability to identify individuals susceptible to metachronous colorectal cancer might ultimately lead to a better prognosis for these patients. The authors suggest that testing for microsatellite instability in (presumably) all primary colorectal cancers may be useful in this regard. However, it is not clear that they have taken sufficient care to exclude patients from families with hereditary non-polyposis colorectal cancer (HNPCC) from their study The inclusion of patients from families with HNPCC would obviously have an effect on the significance of their findings. The authors indicate that none of the individuals in the study group or the control group had any family history of colorectal cancer It would be interesting to know if they interviewed the patients themselves and specifically asked about family history If the information was from a review of the notes, it is a sad fact of life that a full history may not have been taken[1] Furthermore, regardless of the validity of the family history, the authors are wrong to assume that a family history of colorectal cancer is sufficient to exclude a diagnosis of HNPCC. It is clear that many other cancers form part of the spectrum of tumours seen in HNPCC and these should also be taken into account[2]. Clinicians must be aware that families that do not satisfy the strict International Collaborative Group (ICG) guidelines for the diagnosis of HNPCC may still have HNPCC[3] While it is laudable to attempt to identify risk factors for the development of a metachronous colorectal cancer, it is preferable to identify patients particularly at risk of developing the primary cancer. Such patients may be ascertained by a complete and accurate family history. Some of the patients in the study by SenGupta *et al* could have come from families with HNPCC.

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Authors' reply

Sir

We are grateful to Dr Beck for his interest in our paper and agree that information from review of notes may not reflect a full family history. As we had to work from archival tissue we had no alternative method for assessing family history We are aware from Dr Beck's own paper[1] and others[2–4] that patients with colorectal cancer from families that do not fulfill the ICG guidelines for the diagnosis of HNPCC, may nevertheless carry germline mutations in the DNA mismatch repair genes. Conversely, some patients who can be defined as having HNPCC by family history have colorectal cancers which do not show microsatellite instability and lack germline mutations in *hMSH2* and *hMLH1*[3]. Although it is well known that metachronous colorectal cancers are a common feature of patients with HNPCC[5], our study is the first to specifically investigate metachronous colorectal cancers and demonstrate microsatellite instability as a characteristic feature. Indeed, the microsatellite instability status of the index and metachronous cancers was always the same, suggesting that there may be an underlying inherited cause for these metachronous cancers. We have not ruled out the possibility that the patients may have inherited mutations in the DNA mismatch repair genes and have HNPCC (unpublished results). We have merely pointed out that the known family history and age range of the patients is unlike that reported for HNPCC in general. Furthermore, the level of microsatellite instability (number of loci involved) is lower than that normally demonstrated for cancers from patients with HNPCC. This has also been shown by Cawkwell *et al.*[6] and may suggest the involvement of mismatch repair genes other than those presently found to cause HNPCC. In fact, even in families that conform to the ICG criteria for HNPCC there appears to be no obvious genotype to phenotype relationship for this disease[7], indicating that unlinked modifier genes and environmental factors may also play a role. A complete and accurate family history may bias risk against those who are susceptible to metachronous colorectal cancers but do not have a family history suggestive of HNPCC. Our study highlights the importance of microsatellite instability status as an independent risk factor for the development of metachronous colorectal cancers.

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Flow cytometric analysis of p53 oncoprotein expression in cutaneous melanoma

Sir

Messrs Ross and Wilson (*Br J Surg* 1997; 84: 803–7) analysed levels of p53 protein in cutaneous melanoma by immunofluorescent staining and flow cytometry and describe a possible causal relationship between loss of wild type p53 function and growth deregulation leading to ulceration. No difference in p53 levels between primary and metastatic melanoma were detected.

The assay used assumed that an increase in the level of p53 protein was due to the presence of *p53* gene mutations which result in an oncoprotein that is less prone to degradation than the non-mutated counterpart. The greater stabilization of the mutated gene product results in an increase in its steady state level at which it can be identified by standard immunohistochemical means. This is in contrast to the normal cellular levels of wild type p53 which are insufficient for immunohistochemical detection[1].

There are a number of potential errors in this assumption leading to false-positive and -negative results. The most common cause for a false-negative result occurs when a mutated protein is not immunologically recognized by the antibody because of loss of the antigenic domain, for example, in some sarcomas when a *p53* mutation is a gross deletion or a nonsense mutation, leading to a greatly altered protein structure[2].

A false-positive result may occur as the antibody used does not distinguish between wild type and mutant p53 protein and the occurrence of a small number of strongly staining cells may result from the presence of increased levels of functioning, wild type p53 as a normal response to an accumulation of DNA damage occurring in a subpopulation of tumour cells. The authors cite ranges of positive staining from 0·4 (mean 6·3) per cent of cells in a given tumour for primary melanomas measuring less than 3 mm.

In addition, the steady state levels of p53 can be secondary to the altered function of other associated proteins. The stabilization of p53, and consequently the regulation of its tumour suppressor activity, is intimately related via an autoregulatory feedback loop to the functioning of the *mdm2* gene product. Although increased levels of p53 may result the causal mutation may be attributed to an alternative gene such as *mdm2*[3].

This assay, when used alone, is not sufficient to identify a causal role for *p53* mutations in phenotypic progression. Mutational analysis such as sequencing commonly mutated exons or those implicated by single strand conformational polymorphism would be required. Furthermore, flow cytometry as a means of assessing immunohistochemical staining in tissues (as opposed to cell culture conditions) is arguably no more useful than standard microscopy. The benefits of rapidity of analysis and quantification are offset by the loss of cellular localization of protein, which can be an important indicator of the presence of a mutation[4], and by the requirement for lengthy tissue preparation before staining with antibody. To demonstrate a statistically valid prognostic correlation between p53 staining and outcome would require no fewer samples than would be the case if standard immunohistochemical scoring were to be used.

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Authors' reply

Sir

We welcome the opportunity of reaffirming the established view[1] that stabilization of the p53 protein, and its detection, is not dependent on *p53* gene mutation. Our paper makes no assumption of a causal relationship between oncoprotein detection and gene mutation as no mutation analysis was performed or alluded to. We also stated that 'detection of p53 protein is unlikely to follow clonal mutation in the *p53* gene'.

Greenblatt *et al.*[2] found *p53* mutations in only 9 per cent of melanomas following analysis of exons 5 to 8. Florens *et al.*[3] subsequently investigated *p53* gene mutation and expression of the encoded messenger RNA and oncoprotein and found no obvious association between any of them, suggesting a complex relationship involving considerable post-translational modification

We recognize, and state, that flow cytometry and immunohistochemistry are complementary.

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Bile duct injury following laparoscopic cholecystectomy: referral pattern and management

Sir
We read with interest the article by Mr Mirza and colleagues (*Br J Surg* 1997; 84: 786–90) concerning bile duct injury following laparoscopic cholecystectomy. In the discussion the authors state that the role of intraoperative cholangiography is unclear 'since most injuries occur as a result of inadvertent clipping and division of the common duct that has been mistaken for the cystic duct'. Indeed, these accidents are often related to aberrant biliary anatomy, which occurs in around 15 per cent of the population[1]. It is, however, surprising that the authors do not mention intravenous cholangiography (IVC) as an alternative imaging tool, or even quote our paper or any other recent publication regarding IVC[2,3]. This technique, which declined in the 1980s, has gained new popularity in the 1990s as laparoscopic cholecystectomy and its well recognized complications have become commoner, and as safer contrast media have been developed[2–4]. Preoperative IVC represents a reliable, safe, cheap alternative to both endoscopic retrograde cholangiopancreatography and intraoperative cholangiography to assess biliary tract anatomy in patients candidate to laparoscopic cholecystectomy.

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Authors' reply

Sir
We are pleased that our paper stimulated the interest of Mr Basso and colleagues.

Our point on the role of intraoperative cholangiography being unclear relates to the fact that by the time cholangiography has been performed, the common bile duct has often already been damaged. We suggest that the main role of operative cholangiography is to investigate the anatomy rather than the state of the bile duct for stones or other pathology.

It is for this reason that we did not mention intravenous cholangiography, the purpose of which is to detect stones or other pathology before laparoscopic cholecystectomy. Prior intravenous cholangiography does not usually help in the identification of structures during surgery and avoid the disaster of a major bile duct injury.

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British Journal of Surgery 1997, 84, 1753–1754

Book reviews

Pathology and Surgery of the Salivary Glands

R A. Cawson, M. J. Gleeson and J. W. Eveson. 282 × 224 mm. Pp 238. Illustrated. 1997. Oxford. Isis Medical Media. £130.

Diseases of salivary glands form part of the subject matter for postgraduate students studying for higher surgical qualifications. It has been regarded as a mysterious domain of eponymous diagnosis, for example, Sjogren's syndrome, Castelman's disease, and of tumours with unusual features such as perineural spread or a propensity for seeding. This new book is beautifully presented with excellent colour illustrations, large prints and a most attractive layout. There are nine chapters and the last of 38 pages deals with surgery. The book is not a reference text but informative, light and easy to read. The chapters are arranged with a clinical description of the disorder, microscopy and treatment The subject is aproached from the viewpoint of pathology with its attendant classifications based on histology; this is not surprising as two of the authors are pathologists The only reservation after reading this elegantly presented work is that there is not more emphasis on practical issues of how to establish a likely diagnosis preliminary to the all important problem of treatment in a patient with a particular salivary complaint. This volume is perhaps the best available to meet the needs of postgraduate students studying for higher qualifications.

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Innovations in Urologic Surgery

R. Hohenfellner (ed.). 282 × 226 mm. Pp. 645. Illustrated. 1997. Oxford: Isis Medical Media. £150.

Over the past decade, certain advances in urological surgery have irretrievably altered patient management. Percutaneous treatment of renal stone disease has all but consigned open stone surgery to the history book, combined chemotherapy and surgery for advanced testis cancer have resulted in cure for most patients, and new technology is threatening to replace conventional prostatectomy for benign disease. The title of this book is a misnomer for it covers none of these treatments, but is rather a personal selection of many complex open urological procedures that are used frequently in only major centres; it deliberately excludes many standard procedures and many procedures are not truly 'innovations'. The book was originally published in a German version in 1994 and has been revised extensively. Although there are a number of international authors, the work is essentially a distillation of the accumulated skills and wisdom of Professor Rudi Hohenfellner who, until his recent retirement, headed the university urological department in Mainz. For many years this department has been the main European destination for urologists young and old who wished to see at first hand one of the finest academic and clinical urological units.

I enjoyed the book for it provides in one volume detailed descriptions and 'tricks of the trade' of many complex adult and paediatric urological procedures that have been evaluated in Mainz; I shall undoubtedly use it regularly. It will be of great use to the subspecialist and to urological trainees in their final years who are learning to carry out difficult and complex open surgery. The text is well produced by Isis; most illustrations are in black and white.

I have some criticisms, many of which are minor and almost inherent in the nature of the book which has the major merit of being based largely on personal experience culled over many years in a single centre. Nevertheless, worldwide, the urological subspecialist working in large centres will be performing only a selection of the procedures described in this volume, but not all the complex open procedures within a single subspecialty area are described. My personal opinion is that such large reference textbooks of operative urology will be replaced by texts aimed at the subspecialist, perhaps including a CD-ROM covering video clips of difficult procedures. There is, for instance, no section on artificial sphincter implantation, reconstruction of the female urethra or ureteric replacement. Some operations such as bladder reduction plasty and operations for the 'nutcracker phenomenon' do not have widespread acceptance and are not new procedures. Operations such as reconstruction of the ileocaecal valve following the use of the ileocaecal segment for bladder reconstruction are still experimental, while others, including radical nephrectomy, will be done by many general urologists. Most experienced reconstructive surgeons who have had the experience of regularly removing urinary stones that have formed on metal staples used in bladder reconstruction would seriously question the use of staples at all in tissues that are in contact with urine Some illustrations could be labelled more clearly; I was uncertain of the orientation in some of them, even in procedures I do regularly. On a minor note, the direction that the puboprostatic ligament is being divided by scissors in the performance of a radical prostatectomy would be very likely to damage the dorsal vein complex Despite these comments, the book will be warmly welcomed and used by the senior trainee and the subspecialist urologist working in a large centre because of the accumulated wisdom of the master surgeons set out clearly in text and figure. There will be heavy use of the copy that is placed next to my urological theatre.

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Textbook of Endocrine Surgery

O. H Clark and Quan-Yang Duh. 285 × 220 mm. Pp. 195. Illustrated. 1997. Philadelphia, Pennsylvania: W. B. Saunders. £104.

This is an extremely comprehensive text which will be welcomed by specialist endocrine surgeons, consultant general surgeons and surgical trainees alike. For the endocrine surgeon, the book represents a high-quality source of detailed current information and opinion on the full spectrum of endocrine surgical disease and its appropriate management, for the others it will serve as an invaluable reference base for specific topics in the field. The volume is well set out in four sections, simply titled 'Thyroid', 'Parathyroid', 'Adrenal' and 'Pancreas'. The authorship is truly international and encompasses all of those recognized as authorities in endocrine surgery from around the world.

The chapters vary in type from 'General Overview' to those addressing very specific topics. Pleasingly, in dealing with certain controversial subjects, such as the surgical management of papillary carcinoma of thyroid and the operative strategy in primary hyperparathyroidism, separate chapters documenting the differing alternative opinions have been included. Chapters dealing with topics such as the recently characterized genetic abnormality in the multiple endocrine neoplasia type 2 syndrome and familial medullary thyroid carcinoma, and laparoscopic adrenalectomy are testament to the 'state-of-the-art' nature of the text. Basic science is not forgotten and each section is introduced by one or more chapters covering the embryology, physiology and anatomy of the various endocrine glands, but written by practising surgeons. The text is well set out and the tables, illustrations and figures are clear and relevant. The fact that the clinical photographs are printed in black and white has, in the majority of instances, resulted in no loss of impact. In summary, this is a high-quality, 'state-of-the-art' textbook of endocrine surgery which is a 'must' for any surgeon with a major endocrine interest and which will undoubtedly become a standard reference volume on medical library shelves throughout the world.

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Management of Gastrointestinal Cancer

P. McCulloch and A. Kingsnorth (eds). 240 × 162 mm. Pp 404. Illustrated. 1996. London: BMJ Publishing Group. £75.

This book has been aimed as a practical tome for specialists dealing with gastrointestinal cancers using a modern integrated interdisciplinary team approach. To meet this objective the editors have obtained contributions from both surgeons experienced in the management of such tumours and medical or radiation oncological specialists with their own expertise in this area. An added unique feature is the contribution from Japanese surgeons whose approaches to gastrointestinal tumours are more aggressive than those of most in the UK. These contributions reveal how their alternative understanding of tumour spread affects management and results. The book opens with sections on epidemiology, biology and molecular aspects of all gastrointestinal tumours, before moving on to discuss individual tumour sites in greater detail. There is a final chapter on lymphomas. Inevitably there are some areas of overlap between the individual contributions but this has been minimized by careful editing and, where it occurs, it acts as a useful reminder of the topic. Overall, this is an excellent reference book that should certainly find its place in the libraries of hospitals providing cancer services in this area. In addition, any trainee would find it invaluable in preparing for specialist examinations in gastroenterology.

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Notices and announcements

25 February–1 March 1998
IX Asean Congress of Plastic Surgery
Penang, Malaysia
Information: M. Subramaniam, Department of Plastic Surgery, Hospital Ipoh, 30990 Ipoh, Perak, Malaysia

26–27 March 1998
3rd M62 Coloproctology Course
Manchester, UK
Information: J. Hill, Department of General and Colorectal Surgery, Central Manchester Healthcare Trust, Oxford Road, Manchester M13 9WL, UK

20–22 April 1998
The Paediatric Oesophagus. An Interdisciplinary Symposium. Main Topic: Gastro-Oesophageal Reflux with a Special Interest in Alkaline Reflux
Izmir, Turkey
Information: O Mutaf, Department of Paediatric Surgery, Ege University Faculty of Medicine, 35100 Izmir, Turkey

13–15 May 1998
Association of Surgeons of Great Britain and Ireland
Edinburgh, UK
Information: Association of Surgeons of Great Britain and Ireland, The Royal College of Surgeons of England, 35–43 Lincoln's Inn Fields, London WC2A 3PN, UK

20–24 June 1998
Therapeutic Options for the Locally Advanced Non-Small Cell Lung Cancer
Terme di Valdieri, Italy
Information. G. Buccheri, Scientific Secretary, Ospedale A. Carle, 1-12100 Roccavione (CN), Italy

12–17 July 1998
XVII World Congress of the Transplantation Society
Montréal, Canada
Information. L. Felicissimo and Associates, 12449 rue Cousineau, Montréal, Québec, Canada H4K 1P9

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The Editorial Board of *The British Journal of Surgery* encourages submission of review articles on topics of interest to its readers. Any topic will be considered, but priority will be given to those addressing a major current problem. The author of each accepted review will receive an honorarium. Potential authors seeking advice on the suitability of review topics are advised to contact· Mr J. A Murie, University Department of Surgery, The Royal Infirmary, Edinburgh EH3 9YW, UK.

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Manuscripts must be clearly reproduced with adequate space for editorial notes. **Type or print the text on one side of sheets of A4 paper (210 × 297 mm) with double spacing and 4-cm margins. Manuscripts that do not conform to these requirements will be returned to you for recasting.** Begin each section (abstract, introduction, patients and methods, results, and discussion) on a new page.

Title page

On the title page give. (1) the title of the article; (2) the name and initials of each author; (3) the department and institution to which the work should be attributed; (4) the name, address, and telephone, facsimile and e-mail numbers of the author responsible for correspondence and to whom requests for reprints should be addressed; (5) sources of financial support; and (6) the category in which the manuscript is being submitted (original article, review etc.).

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This should be not more than 200 words on the second page of the manuscript and be presented in a structured format **Background:** state why the study was done, and its main aim; **Method:** describe patients, laboratory material and other methods used. Clearly identify the nature of the study: randomized controlled trial, retrospective review, experimental study, etc **Results:** state the main findings of the study; include important numerical values. **Conclusion:** state the main conclusion drawn from the results. Controversial or unexpected observations may be highlighted, but keep this section brief. Write the abstract in clear prose

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Statistics

For detailed guidance on the handling of statistical material, consult *Br J Surg* 1991; 78: 782–4. In evaluating a manuscript the Editors and statistical referees will consider the design of the study, the presentation and analysis of data and the interpretation of results.

Design

Set out clearly the objectives of the study, identify the primary and secondary hypotheses, and the chosen end-points, and explain the rationale for the choice of sample size Investigators embarking on randomized controlled studies may wish to consider the CONSORT statement (*JAMA* 1996; 276: 637–9).

Presentation

Whenever possible use graphical presentation to illustrate the main findings of a study The use of standard deviation and standard error should be clearly distinguished Do not use the '±' symbol; these statistics should be presented in parentheses after the mean value

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Clearly describe which methods were used for which analyses, any methods not in common usage should be supported by references. Report results of statistical tests by stating the value of the test statistic, the number of degrees of freedom and the P value, e g. '$t = 1{\cdot}34$, 16 d.f., $P = 0{\cdot}20$'.

Actual P values should be reported to two decimal places, especially when the result is not significant, rather than stating 'not significant'. Whenever possible, the results of the primary analyses should be reported using confidence intervals instead of, or in addition to, P values.

Interpretation

Do not confuse statistical significance with clinical significance In particular, 'negative' findings should be interpreted through the use of confidence intervals.

Beware of placing undue emphasis on secondary analyses, especially when they are suggested by an inspection of the data.

References

Type the references with double spacing in the Vancouver style (see above: Uniform Requirements for Manuscripts Submitted to Biomedical Journals). Reference to abstracts from meetings is discouraged. Reference to unpublished communications will not be accepted. Cite personal communications in the text, in parentheses. The first author is responsible for confirming the acceptability of the material quoted with the originator.

In the text, number the references consecutively by superscript: ^{1} or $^{1-3}$. References cited only in tables or figures should be numbered in sequence according to the first mention of the table or figure in the text. The sequence for a standard journal article should be· author(s); title of paper, journal name abbreviated as in Index Medicus (written in full if no abbreviation is quoted); year of publication; volume number, page numbers. For example: De Bolla AR, Obeid ML. Mortality in acute pancreatitis. *Ann R Coll Surg Engl* 1984; 66: 184–6. The sequence for the chapters of a book should be: author(s); chapter title; editors; book title, place of publication; publisher; year of publication; page numbers For example: Calenoff L, Rogers L. Esophageal complications of surgery and lifesaving procedures. In· Meyers M, Ghahremani G, eds. *Iatrogenic Gastrointestinal Complications*. New York: Springer, 1981: 123–63.

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